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(54) **ISOQUINOLIN-3-YL CARBOXAMIDES AND PREPARATION AND USE THEREOF**

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(58) **Field of Classification Search**

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See application file for complete search history.

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(57) **ABSTRACT**

Isoquinoline compounds for treating various diseases and pathologies are disclosed. More particularly, the present disclosure concerns the use of an isoquinoline compound or analogs thereof, in the treatment of disorders characterized by the activation of Wnt pathway signaling (e.g., cancer, abnormal cellular proliferation, angiogenesis, Alzheimer's disease, lung disease, inflammation, auto-immune diseases and osteoarthritis), the modulation of cellular events mediated by Wnt pathway signaling, as well as neurological conditions/disorders/diseases linked to overexpression of DYRK1A.

30 Claims, No Drawings

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ISOQUINOLIN-3-YL CARBOXAMIDES AND PREPARATION AND USE THEREOF

RELATED APPLICATIONS

This application is a continuation application of U.S. application Ser. No. 15/498,990, filed Apr. 27, 2017, and claims the benefit of U.S. Provisional Application No. 62/328,210, filed Apr. 27, 2016, each of which is incorporated herein by reference in its entirety.

BACKGROUND

Technical Field

This disclosure relates to inhibitors of one or more proteins in the Wnt pathway, including inhibitors of one or more Wnt proteins, and compositions comprising the same. More particularly, it concerns the use of an isoquinoline compound or salts or analogs thereof, in the treatment of disorders characterized by the activation of Wnt pathway signaling (e.g., cancer, abnormal cellular proliferation, angiogenesis, Alzheimer's disease, lung disease, inflammation, auto-immune diseases fibrotic disorders, cartilage (chondral) defects, and osteoarthritis), the modulation of cellular events mediated by Wnt pathway signaling, as well as genetic diseases and neurological conditions/disorders/diseases due to mutations or dysregulation of the Wnt pathway and/or of one or more of Wnt signaling components. Also provided are methods for treating Wnt-related disease states, as well as neurological conditions/disorders/diseases linked to overexpression of DYRK1A.

Background

The Wnt growth factor family includes more than 10 genes identified in the mouse and at least 19 genes identified in the human. Members of the Wnt family of signaling molecules mediate many short- and long-range patterning processes during invertebrate and vertebrate development. The Wnt signaling pathway is known for its role in the inductive interactions that regulate growth and differentiation, and it also plays roles in the homeostatic maintenance of post-embryonic tissue integrity. Wnt stabilizes cytoplasmic β-catenin, which stimulates the expression of genes including c-myc, c jun, fra-1, and cyclin D1. In addition, misregulation of Wnt signaling can cause developmental defects and is implicated in the genesis of several human cancers. The Wnt pathway has also been implicated in the maintenance of stem or progenitor cells in a growing list of adult tissues including skin, blood, gut, prostate, muscle, and the nervous system.

Dual specificity tyrosine-phosphorylation-regulated kinase 1A is an enzyme that in humans is encoded by the DYRK1A gene. DYRK1A is a member of the dual-specificity tyrosine phosphorylation-regulated kinase (DYRK) family. DYRK1A contains a nuclear targeting signal sequence, a protein kinase domain, a leucine zipper motif, and a highly conservative 13-consecutive-histidine repeat. It catalyzes its autophosphorylation on serine/threonine and tyrosine residues. It may play a significant role in a signaling pathway regulating cell proliferation and may be involved in brain development. DYRK1A is localized in the Down syndrome critical region of chromosome 21, and is considered to be a candidate gene for learning defects associated with Down syndrome. DYRK1A is also expressed in adult brain neurons, indicating that DYRK1A may play a role in the mature central nervous system. Thus, several lines of evidence point to some synaptic functions of DYRK1A. For instance, it has been found that DYRK1A phosphorylates and modulates the interaction of several components of the endocytic protein complex machinery (Dynamin 1, Amphiphysin, and Synaptojanin), suggesting a role in synaptic vesicle recycling. In addition, a polymorphism (SNP) in DYRK1A was found to be associated with HIV-1 replication in monocyte-derived macrophages, as well as with progression to AIDS in two independent cohorts of HIV-1-infected individuals.

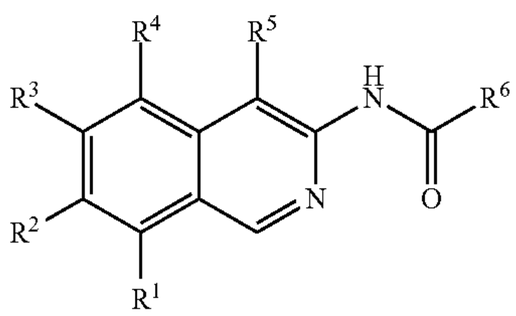
SUMMARY

The present disclosure provides methods and reagents, involving contacting a cell with an agent, such as an isoquinoline compound, in a sufficient amount to antagonize a Wnt activity, e.g., to reverse or control an aberrant growth state or correct a genetic disorder due to mutations in Wnt signaling components.

The present disclosure also provides methods and reagents, involving contacting a cell with an agent, such as an isoquinoline compound, in a sufficient amount to antagonize DYRK1A activity, e.g., i) to normalize prenatal and early postnatal brain development; ii) to improve cognitive function in youth and adulthood; and/or iii) to attenuate Alzheimer's-type neurodegeneration.

Some embodiments disclosed herein include Wnt and/or DYRK1A inhibitors containing an isoquinoline core. Other embodiments disclosed herein include pharmaceutical compositions and methods of treatment using these compounds.

One embodiment disclosed herein includes a compound having the structure of Formula I:



I

as well as prodrugs and pharmaceutically acceptable salts thereof.

In some embodiments of Formula (I):

R^1, R^2, R^4, and R^5 are independently selected from the group consisting of H, halide, unsubstituted —(C_{1-3} haloalkyl), and unsubstituted —(C_{1-3} alkyl);

R^3 is a 5-membered heteroaryl optionally substituted with 1-4 R^{45};

R^6 is selected from the group consisting of —(C_{1-4} alkylene)$_p$heterocyclyl optionally substituted with 1-10 R^{36}, —(C_{1-4} alkylene)$_p$carbocyclyl optionally substituted with 1-12 R^{37}, —(C_{1-4} alkylene)$N(R^{46})(R^{47})$, and —$CF(C_{1-9}$ alkyl)$_2$; wherein each alkyl of —$CF(C_{1-9}$ alkyl)$_2$ is, independently, optionally substituted with one or more halides; wherein each —(C_{1-4} alkylene) is, independently, optionally substituted with one or more substituents as defined anywhere herein;

each R^{36} is independently selected from the group consisting of halide, unsubstituted —(C_{1-9} alkyl), unsubstituted —(C_{2-9} alkenyl), unsubstituted —(C_{2-9} alkynyl), unsubstituted —(C_{1-9} haloalkyl), —(C_{1-4} alkylene)$_p$$OR^{42}$, —($C_{1-4}$ alkylene)$_p$heterocyclyl optionally substituted with 1-10 R^{43},

and —(C_{1-4} alkylene)$_p$carbocyclyl optionally substituted with 1-12 R^{44}; wherein each —(C_{1-4} alkylene) is, independently, optionally substituted with one or more substituents as defined anywhere herein;

each R^{37} is independently selected from the group consisting of halide, unsubstituted —(C_{1-9} alkyl), unsubstituted —(C_{2-9} alkenyl), unsubstituted —(C_{2-9} alkynyl), unsubstituted —(C_{1-9} haloalkyl), —(C_{1-4} alkylene)$_p$OR^{42}, —(C_{1-4} alkylene)$_p$heterocyclyl optionally substituted with 1-10 R^{43}, and —(C_{1-4} alkylene)$_p$carbocyclyl optionally substituted with 1-12 R^{44}; wherein each —(C_{1-4} alkylene) is, independently, optionally substituted with one or more substituents as defined anywhere herein;

each R^{38} is independently selected from the group consisting of halide, unsubstituted —(C_{1-5} alkyl), unsubstituted —(C_{2-5} alkenyl), unsubstituted —(C_{2-5} alkynyl), unsubstituted —(C_{1-5} haloalkyl), —CN, and —(C_{1-4} alkylene)$_p$carbocyclyl optionally substituted with 1-12 R^{44}; wherein each —(C_{1-4} alkylene) is, independently, optionally substituted with one or more substituents as defined anywhere herein;

each R^{39} independently is selected from the group consisting of halide, unsubstituted —(C_{1-5} alkyl), unsubstituted —(C_{2-5} alkenyl), unsubstituted —(C_{2-5} alkynyl), unsubstituted —(C_{1-5} haloalkyl), —CN, and —(C_{1-4} alkylene)$_p$carbocyclyl optionally substituted with 1-12 R^{44}; wherein each —(C_{1-4} alkylene) is, independently, optionally substituted with one or more substituents as defined anywhere herein;

each R^{40} is independently selected from the group consisting of halide, unsubstituted —(C_{1-5} alkyl), unsubstituted —(C_{2-5} alkenyl), unsubstituted —(C_{2-5} alkynyl), unsubstituted —(C_{1-5} haloalkyl), —CN, and —(C_{1-4} alkylene)$_p$carbocyclyl optionally substituted with 1-12 R^{44}; wherein each —(C_{1-4} alkylene) is, independently, optionally substituted with one or more substituents as defined anywhere herein;

each R^{41} is independently selected from the group consisting of halide, unsubstituted —(C_{1-5} alkyl), unsubstituted —(C_{2-5} alkenyl), unsubstituted —(C_{2-5} alkynyl), unsubstituted —(C_{1-5} haloalkyl), and —CN;

each R^{42} is independently selected from the group consisting of unsubstituted —(C_{1-5} alkyl), unsubstituted —(C_{2-5} alkenyl), unsubstituted —(C_{2-5} alkynyl), unsubstituted —(C_{1-5} haloalkyl), and —(C_{1-4} alkylene)$_p$carbocyclyl optionally substituted with 1-12 R^{44}; wherein each —(C_{1-4} alkylene) is, independently, optionally substituted with one or more substituents as defined anywhere herein;

each R^{43} is independently selected from the group consisting of halide, unsubstituted —(C_{1-5} alkyl), unsubstituted —(C_{2-5} alkenyl), unsubstituted —(C_{2-5} alkynyl), unsubstituted —(C_{1-5} haloalkyl), —CN, and —(C_{1-4} alkylene)$_p$carbocyclyl optionally substituted with 1-12 R^{44}; wherein each —(C_{1-4} alkylene) is, independently, optionally substituted with one or more substituents as defined anywhere herein;

each R^{44} is independently selected from the group consisting of halide, unsubstituted —(C_{1-5} alkyl), unsubstituted —(C_{2-5} alkenyl), unsubstituted —(C_{2-5} alkynyl), unsubstituted —(C_{1-5} haloalkyl), and —CN;

each R^{45} is independently selected from the group consisting of H, unsubstituted —(C_{1-9} alkyl), unsubstituted —(C_{2-9} alkenyl), unsubstituted —(C_{2-9} alkynyl), unsubstituted —(C_{1-9} haloalkyl), —(C_{1-4} alkylene)$_p$heterocyclyl optionally substituted with 1-10 R^{38}, and -carbocyclyl optionally substituted with 1-12 R^{39}; wherein each —(C_{1-4} alkylene) is, independently, optionally substituted with one or more substituents as defined anywhere herein;

alternatively, two adjacent R^{45} taken together form a ring which is selected from the group consisting of -heterocyclyl optionally substituted with 1-10 R^{40} and -carbocyclyl optionally substituted with 1-12 R^{41};

R^{46} is attached to the nitrogen and is selected from the group consisting of H, unsubstituted —(C_{1-9} alkyl), unsubstituted —(C_{2-9} alkenyl), unsubstituted —(C_{2-9} alkynyl), unsubstituted —(C_{1-9} haloalkyl), —(C_{1-4} alkylene)$_p$heterocyclyl optionally substituted with 1-10 R^{38}, and -carbocyclyl optionally substituted with 1-12 R^{39}; wherein —(C_{1-4} alkylene) is, optionally substituted with one or more substituents as defined anywhere herein;

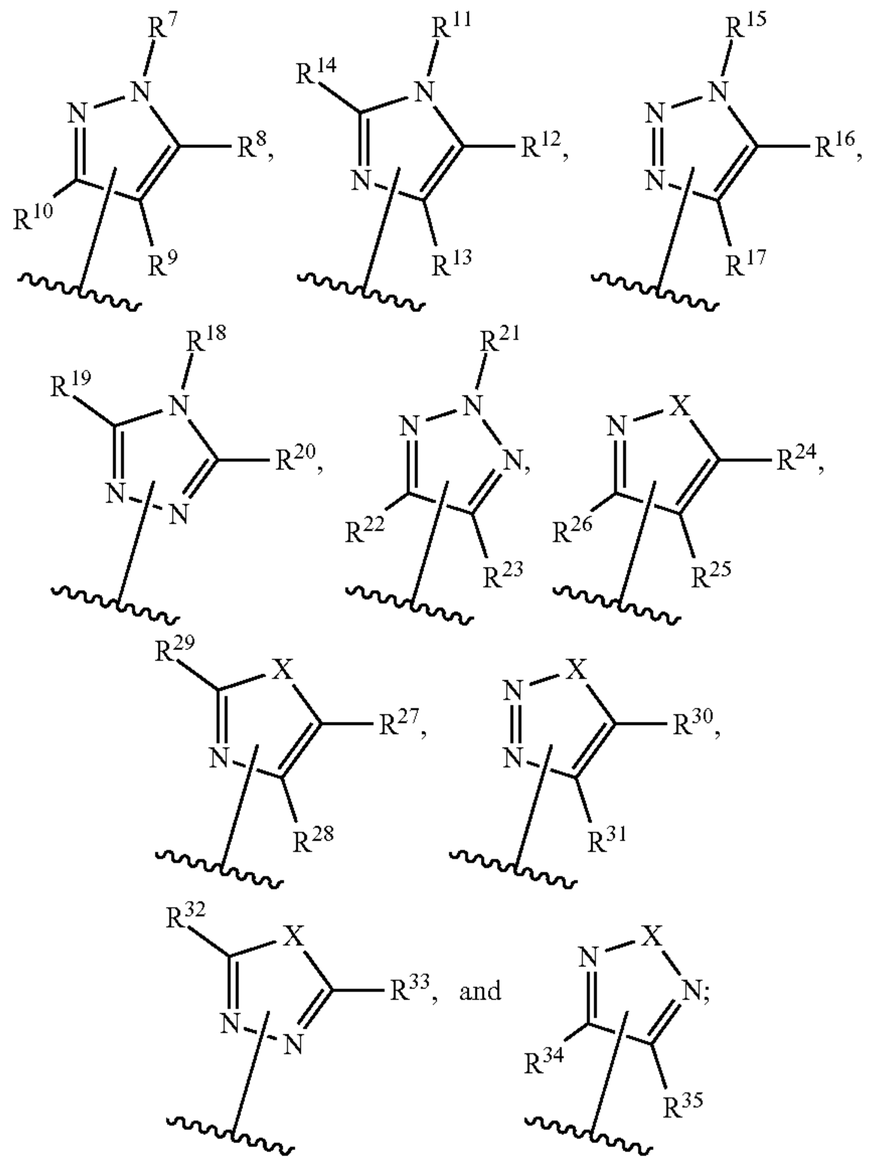
R^{47} is attached to the nitrogen and is selected from the group consisting of unsubstituted —(C_{1-9} alkyl), unsubstituted —(C_{2-9} alkenyl), unsubstituted —(C_{2-9} alkynyl), unsubstituted —(C_{1-9} haloalkyl), —(C_{1-4} alkylene)$_p$heterocyclyl optionally substituted with 1-10 R^{38}, and -carbocyclyl optionally substituted with 1-12 R^{39}; wherein —(C_{1-4} alkylene) is, optionally substituted with one or more substituents as defined anywhere herein;

each p is independently 0 or 1.

In another embodiment of Formula (I):

R^1, R^2, R^4, and R^5 are independently selected from the group consisting of H, halide, unsubstituted —(C_{1-3} haloalkyl), and unsubstituted —(C_{1-3} alkyl);

R^3 is selected from the group consisting of:



wherein each of R^7-R^{35} is, independently, a substituent as defined anywhere herein or a single bond connecting R^3 to the isoquinoline ring; wherein only one of R^7-R^{10} (when present) is a bond, only one of R^{11}-R^{14} (when present) is a bond, only one of R^{15}-R^{17} (when present) is a bond, only one of R^{18}-R^{20} (when present) is a bond, only one of R^{21}-R^{23} (when present) is a bond, only one of R^{24}-R^{26} (when present) is a bond, only one of R^{27}-R^{29} (when present) is a bond, only one of R^{30}-R^{31} (when present) is a bond, only one of R^{32}-R^{33} (when present) is a bond, and only one of R^{34}-R^{35} (when present) is a bond; for purposes of clarification, any

one of the nitrogen atoms attached to R^7, R^{11}, R^{15}, R^{18}, or R^{21} can serve as the point of attachment of R^3 to the isoquinoline ring; likewise, any one of the carbon atoms attached to R^8, R^9, R^{10}, R^{12}, R^{13}, R^{14}, R^{16}, R^{17}, R^{19}, R^{20}, R^{22}, R^{23}, R^{24}, R^{25}, R^{26}, R^{27}, R^{28}, R^{29}, R^{30}, R^{31}, R^{32}, R^{33}, R^{34}, or R^{35} can serve as the point of attachment of R^3 to the isoquinoline ring; so that:

when the nitrogen atom to which R^7 is attached serves as the point of attachment of R^3 to the isoquinoline ring, then R^7 is a single bond connecting R^3 to the isoquinoline ring;

when the carbon atom to which R^8 is attached serves as the point of attachment of R^3 to the isoquinoline ring, then R^8 is a single bond connecting R^3 to the isoquinoline ring;

when the carbon atom to which R^9 is attached serves as the point of attachment of R^3 to the isoquinoline ring, then R^9 is a single bond connecting R^3 to the isoquinoline ring;

when the carbon atom to which R^{10} is attached serves as the point of attachment of R^3 to the isoquinoline ring, then R^{10} is a single bond connecting R^3 to the isoquinoline ring;

when the nitrogen atom to which R^{11} is attached serves as the point of attachment of R^3 to the isoquinoline ring, then R^{11} is a single bond connecting R^3 to the isoquinoline ring;

when the carbon atom to which R^{12} is attached serves as the point of attachment of R^3 to the isoquinoline ring, then R^{12} is a single bond connecting R^3 to the isoquinoline ring;

when the carbon atom to which R^{13} is attached serves as the point of attachment of R^3 to the isoquinoline ring, then R^{13} is a single bond connecting R^3 to the isoquinoline ring;

when the carbon atom to which R^{14} is attached serves as the point of attachment of R^3 to the isoquinoline ring, then R^{14} is a single bond connecting R^3 to the isoquinoline ring;

when the nitrogen atom to which R^{15} is attached serves as the point of attachment of R^3 to the isoquinoline ring, then R^{15} is a single bond connecting R^3 to the isoquinoline ring;

when the carbon atom to which R^{16} is attached serves as the point of attachment of R^3 to the isoquinoline ring, then R^{16} is a single bond connecting R^3 to the isoquinoline ring;

when the carbon atom to which R^{17} is attached serves as the point of attachment of R^3 to the isoquinoline ring, then R^{17} is a single bond connecting R^3 to the isoquinoline ring;

when the nitrogen atom to which R^{18} is attached serves as the point of attachment of R^3 to the isoquinoline ring, then R^{18} is a single bond connecting R^3 to the isoquinoline ring;

when the carbon atom to which R^{19} is attached serves as the point of attachment of R^3 to the isoquinoline ring, then R^{19} is a single bond connecting R^3 to the isoquinoline ring;

when the carbon atom to which R^{20} is attached serves as the point of attachment of R^3 to the isoquinoline ring, then R^{20} is a single bond connecting R^3 to the isoquinoline ring;

when the nitrogen atom to which R^{21} is attached serves as the point of attachment of R^3 to the isoquinoline ring, then R^{21} is a single bond connecting R^3 to the isoquinoline ring;

when the carbon atom to which R^{22} is attached serves as the point of attachment of R^3 to the isoquinoline ring, then R^{22} is a single bond connecting R^3 to the isoquinoline ring;

when the carbon atom to which R^{23} is attached serves as the point of attachment of R^3 to the isoquinoline ring, then R^{23} is a single bond connecting R^3 to the isoquinoline ring;

when the carbon atom to which R^{24} is attached serves as the point of attachment of R^3 to the isoquinoline ring, then R^{24} is a single bond connecting R^3 to the isoquinoline ring;

when the carbon atom to which R^{25} is attached serves as the point of attachment of R^3 to the isoquinoline ring, then R^{25} is a single bond connecting R^3 to the isoquinoline ring;

when the carbon atom to which R^{26} is attached serves as the point of attachment of R^3 to the isoquinoline ring, then R^{26} is a single bond connecting R^3 to the isoquinoline ring;

when the carbon atom to which R^{27} is attached serves as the point of attachment of R^3 to the isoquinoline ring, then R^{27} is a single bond connecting R^3 to the isoquinoline ring;

when the carbon atom to which R^{28} is attached serves as the point of attachment of R^3 to the isoquinoline ring, then R^{28} is a single bond connecting R^3 to the isoquinoline ring;

when the carbon atom to which R^{29} is attached serves as the point of attachment of R^3 to the isoquinoline ring, then R^{29} is a single bond connecting R^3 to the isoquinoline ring;

when the carbon atom to which R^{30} is attached serves as the point of attachment of R^3 to the isoquinoline ring, then R^{30} is a single bond connecting R^3 to the isoquinoline ring;

when the carbon atom to which R^{31} is attached serves as the point of attachment of R^3 to the isoquinoline ring, then R^{31} is a single bond connecting R^3 to the isoquinoline ring;

when the carbon atom to which R^{32} is attached serves as the point of attachment of R^3 to the isoquinoline ring, then R^{32} is a single bond connecting R^3 to the isoquinoline ring;

when the carbon atom to which R^{33} is attached serves as the point of attachment of R^3 to the isoquinoline ring, then R^{33} is a single bond connecting R^3 to the isoquinoline ring;

when the carbon atom to which R^{34} is attached serves as the point of attachment of R^3 to the isoquinoline ring, then R^{34} is a single bond connecting R^3 to the isoquinoline ring;

when the carbon atom to which R^{35} is attached serves as the point of attachment of R^3 to the isoquinoline ring, then R^{35} is a single bond connecting R^3 to the isoquinoline ring;

R^6 is selected from the group consisting of —(C_{1-4} alkylene)$_p$heterocyclyl optionally substituted with 1-10 R^{36}, —(C_{1-4}alkylene)$_p$carbocyclyl optionally substituted with 1-12 R^{37}, —(C_{1-4} alkylene)$N(R^{46})(R^{47})$, and —$CF(C_{1-9}$ alkyl$)_2$; wherein each alkyl of —$CF(C_{1-9}$ alkyl$)_2$ is, independently, optionally substituted with one or more halides; wherein each —(C_{1-4} alkylene) is, independently, optionally substituted with one or more substituents as defined anywhere herein;

R^7 is selected from the group consisting of a single bond, H, unsubstituted —(C_{1-9} alkyl), unsubstituted —(C_{2-9} alkenyl), unsubstituted —(C_{2-9} alkynyl), unsubstituted —(C_{1-9} haloalkyl), —(C_{1-4} alkylene)$_p$heterocyclyl optionally substituted with 1-10 R^{38}, and -carbocyclyl optionally substituted with 1-12 R^{39}; wherein —(C_{1-4} alkylene) is, optionally substituted with one or more substituents as defined anywhere herein;

R^8, R^9, and R^{10} are independently selected from the group consisting of a single bond, H, halide, unsubstituted —(C_{1-9} alkyl), unsubstituted —(C_{2-9} alkenyl), unsubstituted —(C_{2-9} alkynyl), unsubstituted —(C_{1-9} haloalkyl), —(C_{1-4} alkylene)$_p$heterocyclyl optionally substituted with 1-10 R^{38}, and -carbocyclyl optionally substituted with 1-12 R^{39}; wherein each —(C_{1-4} alkylene) is, independently, optionally substituted with one or more substituents as defined anywhere herein;

alternatively, one of R^7 and R^8, R^8 and R^9, or R^9 and R^{10} are taken together to form a ring which is selected from the group consisting of -heterocyclyl optionally substituted with 1-10 R^{40} and -carbocyclyl optionally substituted with 1-12 R^{41};

R^{11} is selected from the group consisting of a single bond, H, unsubstituted —(C_{1-9} alkyl), unsubstituted —(C_{2-9} alkenyl), unsubstituted —(C_{2-9} alkynyl), unsubstituted —(C_{1-9} haloalkyl), —(C_{1-4} alkylene)$_p$heterocyclyl optionally substituted with 1-10 R^{38}, and -carbocyclyl optionally substituted with 1-12 R^{39}; wherein —(C_{1-4} alkylene) is, optionally substituted with one or more substituents as defined anywhere herein;

R^{12}, R^{13}, and R^{14} are independently selected from the group consisting of a single bond, H, halide, unsubstituted —(C_{1-9} alkyl), unsubstituted —(C_{2-9} alkenyl), unsubstituted —(C_{2-9} alkynyl), unsubstituted —(C_{1-9} haloalkyl), —(C_{1-4} alkylene)$_p$heterocyclyl optionally substituted with 1-10 R^{38}, and -carbocyclyl optionally substituted with 1-12 R^{39}; wherein each —(C_{1-4} alkylene) is, independently, optionally substituted with one or more substituents as defined anywhere herein;

alternatively, one of R^{11} and R^{12}, R^{12} and R^{13}, or R^{14} and R^{11} are taken together to form a ring which is selected from the group consisting of -heterocyclyl optionally substituted with 1-10 R^{40} and -carbocyclyl optionally substituted with 1-12 R^{41};

R^{15} is selected from the group consisting of a single bond, H, unsubstituted —(C_{1-9} alkyl), unsubstituted —(C_{2-9} alkenyl), unsubstituted —(C_{2-9} alkynyl), unsubstituted —(C_{1-9} haloalkyl), —(C_{1-4} alkylene)$_p$heterocyclyl optionally substituted with 1-10 R^{38}, and -carbocyclyl optionally substituted with 1-12 R^{39}; wherein —(C_{1-4} alkylene) is, optionally substituted with one or more substituents as defined anywhere herein;

R^{16} and R^{17} are independently selected from the group consisting of a single bond, H, halide, unsubstituted —(C_{1-9} alkyl), unsubstituted —(C_{2-9} alkenyl), unsubstituted —(C_{2-9} alkynyl), unsubstituted —(C_{1-9} haloalkyl), —(C_{1-4} alkylene)$_p$heterocyclyl optionally substituted with 1-10 R^{38}, and -carbocyclyl optionally substituted with 1-12 R^{39}; wherein each —(C_{1-4} alkylene) is, independently, optionally substituted with one or more substituents as defined anywhere herein;

alternatively, one of R^{15} and R^{16} or R^{16} and R^{17} are taken together to form a ring which is selected from the group consisting of -heterocyclyl optionally substituted with 1-10 R^{40} and -carbocyclyl optionally substituted with 1-12 R^{41};

R^{18} is selected from the group consisting of a single bond, H, unsubstituted —(C_{1-9} alkyl), unsubstituted —(C_{2-9} alkenyl), unsubstituted —(C_{2-9} alkynyl), unsubstituted —(C_{1-9} haloalkyl), —(C_{1-4} alkylene)$_p$heterocyclyl optionally substituted with 1-10 R^{38}, and -carbocyclyl optionally substituted with 1-12 R^{39}; wherein —(C_{1-4} alkylene) is, optionally substituted with one or more substituents as defined anywhere herein;

R^{19} and R^{20} are independently selected from the group consisting of a single bond, H, halide, unsubstituted —(C_{1-9} alkyl), unsubstituted —(C_{2-9} alkenyl), unsubstituted —(C_{2-9} alkynyl), unsubstituted —(C_{1-9} haloalkyl), —(C_{1-4} alkylene)$_p$heterocyclyl optionally substituted with 1-10 R^{38}, and -carbocyclyl optionally substituted with 1-12 R^{39}; wherein each —(C_{1-4} alkylene) is, independently, optionally substituted with one or more substituents as defined anywhere herein;

alternatively, one of R^{18} and R^{19} or R^{18} and R^{20} are taken together to form a heterocyclyl optionally substituted with 1-10 R^{40};

R^{21} is selected from the group consisting of a single bond, H, unsubstituted —(C_{1-9} alkyl), unsubstituted —(C_{2-9} alkenyl), unsubstituted —(C_{2-9} alkynyl), unsubstituted —(C_{1-9} haloalkyl), —(C_{1-4} alkylene)$_p$heterocyclyl optionally substituted with 1-10 R^{38}, and -carbocyclyl optionally substituted with 1-12 R^{39}; wherein —(C_{1-4} alkylene) is, optionally substituted with one or more substituents as defined anywhere herein;

R^{22} and R^{23} are independently selected from the group consisting of a single bond, H, halide, unsubstituted —(C_{1-9} alkyl), unsubstituted —(C_{2-9} alkenyl), unsubstituted —(C_{2-9} alkynyl), unsubstituted —(C_{1-9} haloalkyl), —(C_{1-4} alkylene)$_p$heterocyclyl optionally substituted with 1-10 R^{38}, and -carbocyclyl optionally substituted with 1-12 R^{39}; wherein each —(C_{1-4} alkylene) is, independently, optionally substituted with one or more substituents as defined anywhere herein;

alternatively, R^{22} and R^{23} are taken together to form a ring which is selected from the group consisting of -heterocyclyl optionally substituted with 1-10 R^{40} and -carbocyclyl optionally substituted with 1-12 R^{41};

R^{24}, R^{25}, and R^{26} are independently selected from the group consisting of a single bond, H, halide, unsubstituted —(C_{1-9} alkyl), unsubstituted —(C_{2-9} alkenyl), unsubstituted —(C_{2-9} alkynyl), unsubstituted —(C_{1-9} haloalkyl), —(C_{1-4} alkylene)$_p$heterocyclyl optionally substituted with 1-10 R^{38}, and -carbocyclyl optionally substituted with 1-12 R^{39}; wherein each —(C_{1-4} alkylene) is, independently, optionally substituted with one or more substituents as defined anywhere herein;

alternatively, one of R^{24} and R^{25} or R^{25} and R^{26} are taken together to form a ring which is selected from the group consisting of -heterocyclyl optionally substituted with 1-10 R^{40} and -carbocyclyl optionally substituted with 1-12 R^{41};

R^{27}, R^{28}, and R^{29} are independently selected from the group consisting of a single bond, H, halide, unsubstituted —(C_{1-9} alkyl), unsubstituted —(C_{2-9} alkenyl), unsubstituted —(C_{2-9} alkynyl), unsubstituted —(C_{1-9} haloalkyl), —(C_{1-4} alkylene)$_p$heterocyclyl optionally substituted with 1-10 R^{38}, and -carbocyclyl optionally substituted with 1-12 R^{39}; wherein each —(C_{1-4} alkylene) is, independently, optionally substituted with one or more substituents as defined anywhere herein;

alternatively, R^{27} and R^{28} are taken together to form a ring which is selected from the group consisting of -heterocyclyl optionally substituted with 1-10 R^{40} and -carbocyclyl optionally substituted with 1-12 R^{41};

R^{30} and R^{31} are independently selected from the group consisting of a single bond, H, halide, unsubstituted —(C_{1-9} alkyl), unsubstituted —(C_{2-9} alkenyl), unsubstituted —(C_{2-9} alkynyl), unsubstituted —(C_{1-9} haloalkyl), —(C_{1-4} alkylene)$_p$heterocyclyl optionally substituted with 1-10 R^{38}, and -carbocyclyl optionally substituted with 1-12 R^{39}; wherein each —(C_{1-4} alkylene) is, independently, optionally substituted with one or more substituents as defined anywhere herein;

alternatively, R^{30} and R^{31} are taken together to form a ring which is selected from the group consisting of -heterocyclyl optionally substituted with 1-10 R^{40} and -carbocyclyl optionally substituted with 1-12 R^{41};

R^{32} and R^{33} are independently selected from the group consisting of a single bond, H, halide, unsubstituted —(C_{1-9} alkyl), unsubstituted —(C_{2-9} alkenyl), unsubstituted —(C_{2-9} alkynyl), unsubstituted —(C_{1-9} haloalkyl), —(C_{1-4} alkylene)$_p$heterocyclyl optionally substituted with 1-10 R^{38}, and -carbocyclyl optionally substituted with 1-12 R^{39}; wherein each —(C_{1-4} alkylene) is, independently, optionally substituted with one or more substituents as defined anywhere herein;

R^{34} and R^{35} are independently selected from the group consisting of a single bond, H, halide, unsubstituted —(C_{1-9} alkyl), unsubstituted —(C_{2-9} alkenyl), unsubstituted —(C_{2-9} alkynyl), unsubstituted —(C_{1-9} haloalkyl), —(C_{1-4} alkylene)$_p$heterocyclyl optionally substituted with 1-10 R^{38}, and -carbocyclyl optionally substituted with 1-12 R^{39}; wherein each —(C_{1-4} alkylene) is, independently, optionally substituted with one or more substituents as defined anywhere herein;

alternatively, R^{34} and R^{35} are taken together to form a ring which is selected from the group consisting of -heterocyclyl optionally substituted with 1-10 R^{40} and -carbocyclyl optionally substituted with 1-12 R^{41};

each R^{36} is independently selected from the group consisting of halide, unsubstituted —(C_{1-9} alkyl), unsubstituted —(C_{2-9} alkenyl), unsubstituted —(C_{2-9} alkynyl), unsubstituted —(C_{1-9} haloalkyl), —(C_{1-4} alkylene)$_p$OR^{42}, —(C_{1-4} alkylene)$_p$heterocyclyl optionally substituted with 1-10 R^{43}, and —(C_{1-4} alkylene)$_p$carbocyclyl optionally substituted with 1-12 R^{44}; wherein each —(C_{1-4} alkylene) is, independently, optionally substituted with one or more substituents as defined anywhere herein;

each R^{37} is independently selected from the group consisting of halide, unsubstituted —(C_{1-9} alkyl), unsubstituted —(C_{2-9} alkenyl), unsubstituted —(C_{2-9} alkynyl), unsubstituted —(C_{1-9} haloalkyl), —(C_{1-4} alkylene)$_p$OR^{42}, —(C_{1-4} alkylene)$_p$heterocyclyl optionally substituted with 1-10 R^{43}, and —(C_{1-4} alkylene)$_p$carbocyclyl optionally substituted with 1-12 R^{44}; wherein each —(C_{1-4} alkylene) is, independently, optionally substituted with one or more substituents as defined anywhere herein;

each R^{38} independently is selected from the group consisting of halide, unsubstituted —(C_{1-5} alkyl), unsubstituted —(C_{2-5} alkenyl), unsubstituted —(C_{2-5} alkynyl), unsubstituted —(C_{1-5} haloalkyl), —CN, and —(C_{1-4} alkylene)$_p$carbocyclyl optionally substituted with 1-12 R^{44}; wherein each —(C_{1-4} alkylene) is, independently, optionally substituted with one or more substituents as defined anywhere herein;

each R^{39} is independently selected from the group consisting of halide, unsubstituted —(C_{1-5} alkyl), unsubstituted —(C_{2-5} alkenyl), unsubstituted —(C_{2-5} alkynyl), unsubstituted —(C_{1-5} haloalkyl), —CN, and —(C_{1-4} alkylene)$_p$carbocyclyl optionally substituted with 1-12 R^{44}; wherein each —(C_{1-4} alkylene) is, independently, optionally substituted with one or more substituents as defined anywhere herein;

each R^{40} is independently selected from the group consisting of halide, unsubstituted —(C_{1-5} alkyl), unsubstituted —(C_{2-5} alkenyl), unsubstituted —(C_{2-5} alkynyl), unsubstituted —(C_{1-5} haloalkyl), —CN, and —(C_{1-4} alkylene)$_p$carbocyclyl optionally substituted with 1-12 R^{44}; wherein each —(C_{1-4} alkylene) is, independently, optionally substituted with one or more substituents as defined anywhere herein;

each R^{41} is independently selected from the group consisting of halide, unsubstituted —(C_{1-5} alkyl), unsubstituted —(C_{2-5} alkenyl), unsubstituted —(C_{2-5} alkynyl), unsubstituted —(C_{1-5} haloalkyl), and —CN;

each R^{42} is independently selected from the group consisting of unsubstituted —(C_{1-5} alkyl), unsubstituted —(C_{2-5} alkenyl), unsubstituted —(C_{2-5} alkynyl), unsubstituted —(C_{1-5} haloalkyl), and —(C_{1-4} alkylene)$_p$carbocyclyl optionally substituted with 1-12 R^{44}; wherein each —(C_{1-4} alkylene) is, independently, optionally substituted with one or more substituents as defined anywhere herein;

each R^{43} is independently selected from the group consisting of halide, unsubstituted —(C_{1-5} alkyl), unsubstituted —(C_{2-5} alkenyl), unsubstituted —(C_{2-5} alkynyl), unsubstituted —(C_{1-5} haloalkyl), —CN, and —(C_{1-4} alkylene)$_p$carbocyclyl optionally substituted with 1-12 R^{44}; wherein each —(C_{1-4} alkylene) is, independently, optionally substituted with one or more substituents as defined anywhere herein;

each R^{44} is independently selected from the group consisting of halide, unsubstituted —(C_{1-5} alkyl), unsubstituted —(C_{2-5} alkenyl), unsubstituted —(C_{2-5} alkynyl), unsubstituted —(C_{1-5} haloalkyl), and —CN;

R^{46} is attached to the nitrogen and is selected from the group consisting of H, unsubstituted —(C_{1-9} alkyl), unsubstituted —(C_{2-9} alkenyl), unsubstituted —(C_{2-9} alkynyl), unsubstituted —(C_{1-9} haloalkyl), —(C_{1-4} alkylene)$_p$heterocyclyl optionally substituted with 1-10 R^{38}, and -carbocyclyl optionally substituted with 1-12 R^{39}; wherein —(C_{1-4} alkylene) is, optionally substituted with one or more substituents as defined anywhere herein;

R^{47} is attached to the nitrogen and is selected from the group consisting of unsubstituted —(C_{1-9} alkyl), unsubstituted —(C_{2-9} alkenyl), unsubstituted —(C_{2-9} alkynyl), unsubstituted —(C_{1-9} haloalkyl), —(C_{1-4} alkylene)$_p$heterocyclyl optionally substituted with 1-10 R^{38}, and -carbocyclyl optionally substituted with 1-12 R^{39}; wherein —(C_{1-4} alkylene) is, optionally substituted with one or more substituents as defined anywhere herein;

each X is O or S; and

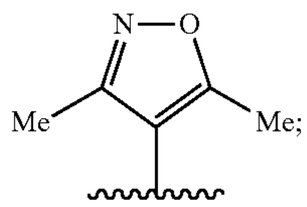
each p is independently 0 or 1.

In another embodiment of Formula (I):

R^1, R^2, R^4, and R^5 are independently selected from the group consisting of H, halide, unsubstituted —(C_{1-3} haloalkyl), and unsubstituted —(C_{1-3} alkyl);

R^3 is a 5-membered heteroaryl optionally substituted with 1-4 R^{45};

with the proviso that R^3 is not



R^6 is selected from the group consisting of —(C_{1-4} alkylene)$_p$heterocyclyl optionally substituted with 1-10 R^{36}, —(C_{1-4} alkylene)$_p$carbocyclyl optionally substituted with 1-12 R^{37}, —(C_{1-4} alkylene)N(R^{46})(R^{47}), —N(R^{48})(R^{49}), —CF(C_{1-9} alkyl)$_2$, —(C_{1-4} alkylene)$_p$O(C_{3-9} alkyl), and —(C_{2-9} alkynyl) optionally substituted with one or more halides; wherein each alkyl of —CF(C_{1-9}alkyl)$_2$ is, independently, optionally substituted with one or more halides; wherein each —(C_{1-4} alkylene) is, independently, optionally substituted with one or more substituents as defined anywhere herein;

with the proviso that R^6 is not unsubstituted —(CH_2) tetrahydropyranyl;

each R^{36} is independently selected from the group consisting of halide, unsubstituted —(C_{1-9} alkyl), unsubstituted —(C_{2-9} alkenyl), unsubstituted —(C_{2-9} alkynyl), unsubstituted —(C_{1-9} haloalkyl), —(C_{1-4} alkylene)$_p$OR^{42}, —(C_{1-4} alkylene)$_p$heterocyclyl optionally substituted with 1-10 R^{43}, —(C_{1-4} alkylene)$_p$carbocyclyl optionally substituted with 1-12 R^{44}, —C(=O)(R^{50}), —(C_{1-4} alkylene)C(=O)OR^{51}, —(C_{1-4} alkylene)aryl optionally substituted with one or more halides, —(C_{1-4} alkylene)$_p$heteroaryl optionally substituted with one or more halides, and —SO_2(R^{52}); wherein each —(C_{1-4} alkylene) is, independently, optionally substituted with one or more substituents as defined anywhere herein;

alternatively, two R^{36} attached to the same carbon atom can together represent =O to form a carbonyl group;

each R^{37} is independently selected from the group consisting of halide, unsubstituted —(C_{1-9} alkyl), unsubstituted —(C_{2-9} alkenyl), unsubstituted —(C_{2-9} alkynyl), unsubstituted —(C_{1-9} haloalkyl), —(C_{1-4} alkylene)$_p$OR^{42}, —N(R^{53})$_2$, —C(=O)(R^{50}), —C(=O)OR^{51}, —(C_{1-4} alkylene)$_p$heterocyclyl optionally substituted with 1-10 R^{43}, and —(C_{1-4} alkylene)$_p$carbocyclyl optionally substituted with

1-12 R^{44}; wherein each —(C_{1-4} alkylene) is, independently, optionally substituted with one or more substituents as defined anywhere herein;

each R^{38} independently is selected from the group consisting of halide, unsubstituted —(C_{1-5} alkyl), unsubstituted —(C_{2-5} alkenyl), unsubstituted —(C_{2-5} alkynyl), unsubstituted —(C_{1-5} haloalkyl), —CN, and —(C_{1-4} alkylene)$_p$carbocyclyl optionally substituted with 1-12 R^{44}; wherein each —(C_{1-4} alkylene) is, independently, optionally substituted with one or more substituents as defined anywhere herein;

each R^{39} is independently selected from the group consisting of halide, unsubstituted —(C_{1-5} alkyl), unsubstituted —(C_{2-5} alkenyl), unsubstituted —(C_{2-5} alkynyl), unsubstituted —(C_{1-5} haloalkyl), —CN, and —(C_{1-4} alkylene)$_p$carbocyclyl optionally substituted with 1-12 R^{44}; wherein each —(C_{1-4} alkylene) is, independently, optionally substituted with one or more substituents as defined anywhere herein;

each R^{40} is independently selected from the group consisting of halide, unsubstituted —(C_{1-5} alkyl), unsubstituted —(C_{2-5} alkenyl), unsubstituted —(C_{2-5} alkynyl), unsubstituted —(C_{1-5} haloalkyl), —CN, and —(C_{1-4} alkylene)$_p$carbocyclyl optionally substituted with 1-12 R^{44}; wherein each —(C_{1-4} alkylene) is, independently, optionally substituted with one or more substituents as defined anywhere herein;

each R^{41} is independently selected from the group consisting of halide, unsubstituted —(C_{1-5} alkyl), unsubstituted —(C_{2-5} alkenyl), unsubstituted —(C_{2-5} alkynyl), unsubstituted —(C_{1-5} haloalkyl), and —CN;

each R^{42} is independently selected from the group consisting of H, unsubstituted —(C_{1-5} alkyl), unsubstituted —(C_{2-5} alkenyl), unsubstituted —(C_{2-5} alkynyl), unsubstituted —(C_{1-5} haloalkyl), and —(C_{1-4} alkylene)$_p$carbocyclyl optionally substituted with 1-12 R^{44}; wherein each —(C_{1-4} alkylene) is, independently, optionally substituted with one or more substituents as defined anywhere herein;

each R^{43} is independently selected from the group consisting of halide, unsubstituted —(C_{1-5} alkyl), unsubstituted —(C_{2-5} alkenyl), unsubstituted —(C_{2-5} alkynyl), unsubstituted —(C_{1-5} haloalkyl), —CN, and —(C_{1-4} alkylene)$_p$carbocyclyl optionally substituted with 1-12 R^{44}; wherein each —(C_{1-4} alkylene) is, independently, optionally substituted with one or more substituents as defined anywhere herein;

each R^{44} is independently selected from the group consisting of halide, unsubstituted —(C_{1-5} alkyl), unsubstituted —(C_{2-5} alkenyl), unsubstituted —(C_{2-5} alkynyl), unsubstituted —(C_{1-5} haloalkyl), —CN, and —(C_{1-4} alkylene)$_p$carbocyclyl optionally substituted with 1-12 R^{44}; wherein each —(C_{1-4} alkylene) is, independently, optionally substituted with one or more substituents as defined anywhere herein;

each R^{45} is independently selected from the group consisting of H, unsubstituted —(C_{1-9} alkyl), unsubstituted —(C_{2-9} alkenyl), unsubstituted —(C_{2-9} alkynyl), unsubstituted —(C_{1-9} haloalkyl), —N(R^{53})$_2$, —(C_{1-4}alkylene)$_p$ OR^{42}, —(C_{1-4} alkylene)$_p$heterocyclyl optionally substituted with 1-10 R^{38}, and -carbocyclyl optionally substituted with 1-12 R^{39}; wherein each —(C_{1-4} alkylene) is, independently, optionally substituted with one or more substituents as defined anywhere herein;

alternatively, two adjacent R^{45} are taken together to form a ring which is selected from the group consisting of -heterocyclyl optionally substituted with 1-10 R^{40} and -carbocyclyl optionally substituted with 1-12 R^{41};

R^{46} is attached to the nitrogen and is selected from the group consisting of H, unsubstituted —(C_{1-9} alkyl), unsubstituted —(C_{2-9} alkenyl), unsubstituted —(C_{2-9} alkynyl), unsubstituted —(C_{1-9} haloalkyl), —(C_{1-4} alkylene)$_p$heterocyclyl optionally substituted with 1-10 R^{38}, and -carbocyclyl optionally substituted with 1-12 R^{39}; wherein —(C_{1-4} alkylene) is, optionally substituted with one or more substituents as defined anywhere herein;

R^{47} is attached to the nitrogen and is selected from the group consisting of unsubstituted —(C_{1-9} alkyl), unsubstituted —(C_{2-9} alkenyl), unsubstituted —(C_{2-9} alkynyl), unsubstituted —(C_{1-9} haloalkyl), —(C_{1-4} alkylene)$_p$heterocyclyl optionally substituted with 1-10 R^{38}, and -carbocyclyl optionally substituted with 1-12 R^{39}; wherein —(C_{1-4} alkylene) is, optionally substituted with one or more substituents as defined anywhere herein;

R^{48} is attached to the nitrogen and selected from the group consisting of H, unsubstituted —(C_{1-5} alkyl), unsubstituted —(C_{2-5} alkenyl), unsubstituted —(C_{2-5} alkynyl), and unsubstituted —(C_{1-5} haloalkyl);

R^{49} is attached to the nitrogen and is selected from the group consisting of —(C_{1-4} alkylene)$_p$heterocyclyl optionally substituted with 1-10 R^{38}, and —(C_{1-4} alkylene)$_p$carbocyclyl optionally substituted with 1-12 R^{39}; wherein each —(C_{1-4} alkylene) is, independently, optionally substituted with one or more substituents as defined anywhere herein;

R^{50} is selected from the group consisting of H, unsubstituted —(C_{3-5} alkyl), unsubstituted —(C_{2-5} alkenyl), unsubstituted —(C_{2-5} alkynyl), unsubstituted —(C_{1-5} haloalkyl), —(C_{1-4} alkylene)$_p$aryl optionally substituted with one or more halides or unsubstituted —(C_{1-5} alkyl), —(C_{1-4} alkylene)$_p$heteroaryl optionally substituted with one or more halides or unsubstituted —(C_{1-5} alkyl), and —(C_{1-4} alkylene)$_p$heterocyclyl optionally substituted with one or more halides or one or more unsubstituted —(C_{1-5} alkyl); wherein each —(C_{1-4} alkylene) is, independently, optionally substituted with one or more substituents as defined anywhere herein;

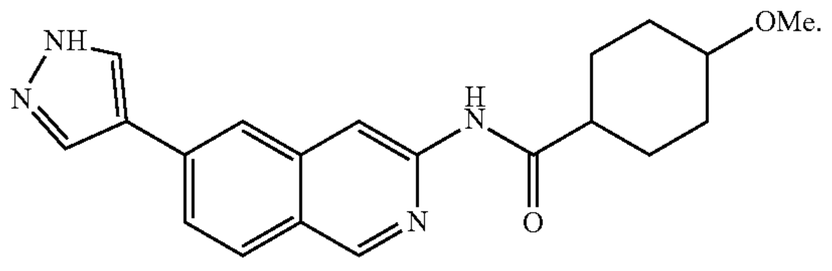
R^{51} is selected from the group consisting of H, unsubstituted —(C_{1-5} alkyl), unsubstituted —(C_{2-5} alkenyl), unsubstituted —(C_{2-5} alkynyl), unsubstituted —(C_{1-5} haloalkyl), —(C_{1-4} alkylene)$_p$aryl optionally substituted with one or more halides or unsubstituted —(C_{1-5} alkyl), —(C_{1-4} alkylene)$_p$heteroaryl optionally substituted with one or more halides or unsubstituted —(C_{1-5} alkyl), and —(C_{1-4} alkylene)$_p$heterocyclyl optionally substituted with one or more halides or one or more unsubstituted —(C_{1-5} alkyl); wherein each —(C_{1-4} alkylene) is, independently, optionally substituted with one or more substituents as defined anywhere herein;

R^{52} is selected from the group consisting of unsubstituted —(C_{1-5} alkyl), unsubstituted —(C_{2-5} alkenyl), unsubstituted —(C_{2-5} alkynyl), unsubstituted —(C_{1-5} haloalkyl), —(C_{1-4} alkylene)$_p$aryl optionally substituted with one or more halides or unsubstituted —(C_{1-5} alkyl), —(C_{1-4} alkylene)$_p$ heteroaryl optionally substituted with one or more halides or unsubstituted —(C_{1-5} alkyl), and —(C_{1-4} alkylene)$_p$heterocyclyl optionally substituted with one or more halides or one or more unsubstituted —(C_{1-5} alkyl); wherein —(C_{1-4} alkylene) is, optionally substituted with one or more substituents as defined anywhere herein;

each R^{53} is independently selected from the group consisting of H, unsubstituted —(C_{1-5} alkyl), unsubstituted —(C_{2-5} alkenyl), and unsubstituted —(C_{2-5} alkynyl);

each p is independently 0 or 1; and

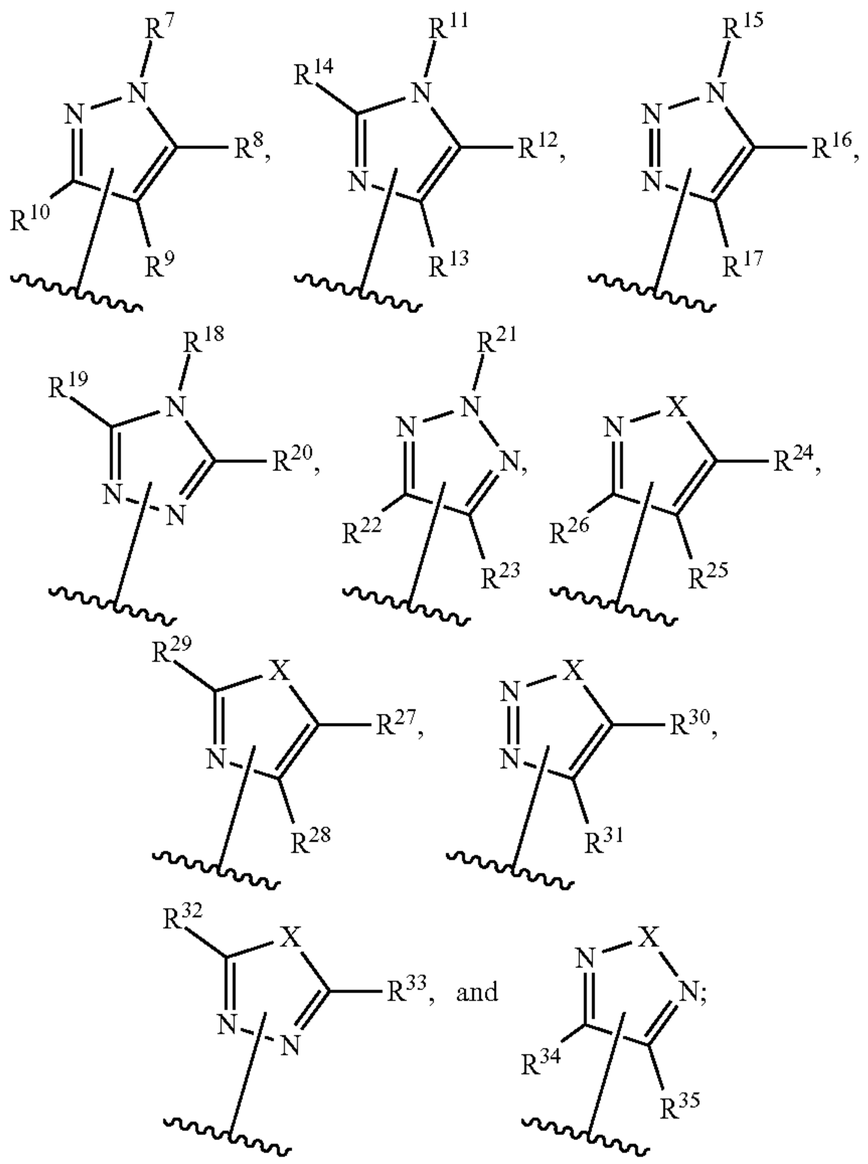
with the proviso that Formula I is not a structure selected from the group consisting of:



In another embodiment of Formula (I):

R^1, R^2, R^4, and R^5 are independently selected from the group consisting of H, halide, unsubstituted —(C_{1-3} haloalkyl), and unsubstituted —(C_{1-3} alkyl);

R^3 is selected from the group consisting of:



wherein each of R^7-R^{35} is, independently, a substituent as defined anywhere herein or a single bond connecting R^3 to the isoquinoline ring; wherein only one of R^7-R^{10} (when present) is a bond, only one of R^{11}-R^{14} (when present) is a bond, only one of R^{15}-R^{17} (when present) is a bond, only one of R^{18}-R^{20} (when present) is a bond, only one of R^{21}-R^{23} (when present) is a bond, only one of R^{24}-R^{26} (when present) is a bond, only one of R^{27}-R^{29} (when present) is a bond, only one of R^{30}-R^{31} (when present) is a bond, only one of R^{32}-R^{33} (when present) is a bond, and only one of R^{34}-R^{35} (when present) is a bond; for purposes of clarification, any one of the nitrogen atoms attached to R^7, R^{11}, R^{15}, R^{18}, or R^{21} can serve as the point of attachment of R^3 to the isoquinoline ring; likewise, any one of the carbon atoms attached to R^8, R^9, R^{10}, R^{12}, R^{13}, R^{14}, R^{16}, R^{17}, R^{19}, R^{20}, R^{22}, R^{23}, R^{24}, R^{25}, R^{26}, R^{27}, R^{28}, R^{29}, R^{30}, R^{31}, R^{32}, R^{33}, R^{34}, or R^{35} can serve as the point of attachment of R^3 to the isoquinoline ring; so that:

when the nitrogen atom to which R^7 is attached serves as the point of attachment of R^3 to the isoquinoline ring, then R^7 is a single bond connecting R^3 to the isoquinoline ring;

when the carbon atom to which R^8 is attached serves as the point of attachment of R^3 to the isoquinoline ring, then R^8 is a single bond connecting R^3 to the isoquinoline ring;

when the carbon atom to which R^9 is attached serves as the point of attachment of R^3 to the isoquinoline ring, then R^9 is a single bond connecting R^3 to the isoquinoline ring;

when the carbon atom to which R^{10} is attached serves as the point of attachment of R^3 to the isoquinoline ring, then R^{10} is a single bond connecting R^3 to the isoquinoline ring;

when the nitrogen atom to which R^{11} is attached serves as the point of attachment of R^3 to the isoquinoline ring, then R^{11} is a single bond connecting R^3 to the isoquinoline ring;

when the carbon atom to which R^{12} is attached serves as the point of attachment of R^3 to the isoquinoline ring, then R^{12} is a single bond connecting R^3 to the isoquinoline ring;

when the carbon atom to which R^{13} is attached serves as the point of attachment of R^3 to the isoquinoline ring, then R^{13} is a single bond connecting R^3 to the isoquinoline ring;

when the carbon atom to which R^{14} is attached serves as the point of attachment of R^3 to the isoquinoline ring, then R^{14} is a single bond connecting R^3 to the isoquinoline ring;

when the nitrogen atom to which R^{15} is attached serves as the point of attachment of R^3 to the isoquinoline ring, then R^{15} is a single bond connecting R^3 to the isoquinoline ring;

when the carbon atom to which R^{16} is attached serves as the point of attachment of R^3 to the isoquinoline ring, then R^{16} is a single bond connecting R^3 to the isoquinoline ring;

when the carbon atom to which R^{17} is attached serves as the point of attachment of R^3 to the isoquinoline ring, then R^{17} is a single bond connecting R^3 to the isoquinoline ring;

when the nitrogen atom to which R^{18} is attached serves as the point of attachment of R^3 to the isoquinoline ring, then R^{18} is a single bond connecting R^3 to the isoquinoline ring;

when the carbon atom to which R^{19} is attached serves as the point of attachment of R^3 to the isoquinoline ring, then R^{19} is a single bond connecting R^3 to the isoquinoline ring;

when the carbon atom to which R^{20} is attached serves as the point of attachment of R^3 to the isoquinoline ring, then R^{20} is a single bond connecting R^3 to the isoquinoline ring;

when the nitrogen atom to which R^{21} is attached serves as the point of attachment of R^3 to the isoquinoline ring, then R^{21} is a single bond connecting R^3 to the isoquinoline ring;

when the carbon atom to which R^{22} is attached serves as the point of attachment of R^3 to the isoquinoline ring, then R^{22} is a single bond connecting R^3 to the isoquinoline ring;

when the carbon atom to which R^{23} is attached serves as the point of attachment of R^3 to the isoquinoline ring, then R^{23} is a single bond connecting R^3 to the isoquinoline ring;

when the carbon atom to which R^{24} is attached serves as the point of attachment of R^3 to the isoquinoline ring, then R^{24} is a single bond connecting R^3 to the isoquinoline ring;

when the carbon atom to which R^{25} is attached serves as the point of attachment of R^3 to the isoquinoline ring, then R^{25} is a single bond connecting R^3 to the isoquinoline ring;

when the carbon atom to which R^{26} is attached serves as the point of attachment of R^3 to the isoquinoline ring, then R^{26} is a single bond connecting R^3 to the isoquinoline ring;

when the carbon atom to which R^{27} is attached serves as the point of attachment of R^3 to the isoquinoline ring, then R^{27} is a single bond connecting R^3 to the isoquinoline ring;

when the carbon atom to which R^{28} is attached serves as the point of attachment of R^3 to the isoquinoline ring, then R^{28} is a single bond connecting R^3 to the isoquinoline ring;

when the carbon atom to which R^{29} is attached serves as the point of attachment of R^3 to the isoquinoline ring, then R^{29} is a single bond connecting R^3 to the isoquinoline ring;

when the carbon atom to which R^{30} is attached serves as the point of attachment of R^3 to the isoquinoline ring, then R^{30} is a single bond connecting R^3 to the isoquinoline ring;

when the carbon atom to which R^{31} is attached serves as the point of attachment of R^3 to the isoquinoline ring, then R^{31} is a single bond connecting R^3 to the isoquinoline ring;

when the carbon atom to which R^{32} is attached serves as the point of attachment of R^3 to the isoquinoline ring, then R^{32} is a single bond connecting R^3 to the isoquinoline ring;

when the carbon atom to which R^{33} is attached serves as the point of attachment of R^3 to the isoquinoline ring, then R^{33} is a single bond connecting R^3 to the isoquinoline ring;

when the carbon atom to which R^{34} is attached serves as the point of attachment of R^3 to the isoquinoline ring, then R^{34} is a single bond connecting R^3 to the isoquinoline ring;

when the carbon atom to which R^{35} is attached serves as the point of attachment of R^3 to the isoquinoline ring, then R^{35} is a single bond connecting R^3 to the isoquinoline ring;

R^6 is selected from the group consisting of —(C_{1-4} alkylene)$_p$heterocyclyl optionally substituted with 1-10 R^{36}, —(C_{1-4} alkylene)$_p$carbocyclyl optionally substituted with 1-12 R^{37}, —(C_{1-4} alkylene)N(R^{46})(R^{47}), —N(R^{48})(R^{49}), —CF(C_{1-9} alkyl)$_2$, —(C_{1-4} alkylene)$_p$O(C_{3-9} alkyl), and —(C_{2-9} alkynyl) optionally substituted with one or more halides; wherein each alkyl of —CF(C_{1-9}alkyl)$_2$ is, independently, optionally substituted with one or more halides; wherein each —(C_{1-4} alkylene) is, independently, optionally substituted with one or more substituents as defined anywhere herein;

with the proviso that R^6 is not unsubstituted —(CH_2) tetrahydropyranyl;

R^7 is selected from the group consisting of a single bond, H, unsubstituted —(C_{1-9} alkyl), unsubstituted —(C_{2-9} alkenyl), unsubstituted —(C_{2-9} alkynyl), unsubstituted —(C_{1-9} haloalkyl), —(C_{1-4} alkylene)OR^{42}, —(C_{1-4} alkylene)$_p$heterocyclyl optionally substituted with 1-10 R^{38}, and -carbocyclyl optionally substituted with 1-12 R^{39}; wherein —(C_{1-4} alkylene) is, optionally substituted with one or more substituents as defined anywhere herein;

R^8, R^9, and R^{10} are independently selected from the group consisting of a single bond, H, halide, unsubstituted —(C_{1-9} alkyl), unsubstituted —(C_{2-9} alkenyl), unsubstituted —(C_{2-9} alkynyl), unsubstituted —(C_{1-9} haloalkyl), —N(R^{53})$_2$, —(C_{1-4} alkylene)$_p$OR^{42}, —(C_{1-4} alkylene)$_p$heterocyclyl optionally substituted with 1-10 R^{38}, and -carbocyclyl optionally substituted with 1-12 R^{39}; wherein each —(C_{1-4} alkylene) is, independently, optionally substituted with one or more substituents as defined anywhere herein;

alternatively, one of R^7 and R^8, R^8 and R^9, or R^9 and R^{10} are taken together to form a ring which is selected from the group consisting of -heterocyclyl optionally substituted with 1-10 R^{40} and -carbocyclyl optionally substituted with 1-12 R^{41};

R^{11} is selected from the group consisting of a single bond, H, unsubstituted —(C_{1-9} alkyl), unsubstituted —(C_{2-9} alkenyl), unsubstituted —(C_{2-9} alkynyl), unsubstituted —(C_{1-9} haloalkyl), —(C_{1-4} alkylene)OR^{42}, —(C_{1-4} alkylene)$_p$heterocyclyl optionally substituted with 1-10 R^{38}, and -carbocyclyl optionally substituted with 1-12 R^{39}; wherein —(C_{1-4} alkylene) is, optionally substituted with one or more substituents as defined anywhere herein;

R^{12}, R^{13}, and R^{14} are independently selected from the group consisting of a single bond, H, halide, unsubstituted —(C_{1-9} alkyl), unsubstituted —(C_{2-9} alkenyl), unsubstituted —(C_{2-9} alkynyl), unsubstituted —(C_{1-9} haloalkyl), —N(R^{53})$_2$, —(C_{1-4} alkylene)$_p$OR^{42}, —(C_{1-4} alkylene)$_p$heterocyclyl optionally substituted with 1-10 R^{38}, and -carbocyclyl optionally substituted with 1-12 R^{39}; wherein each —(C_{1-4} alkylene) is, independently, optionally substituted with one or more substituents as defined anywhere herein;

alternatively, one of R^{11} and R^{12}, R^{12} and R^{13}, or R^{14} and R^{11} are taken together to form a ring which is selected from the group consisting of -heterocyclyl optionally substituted with 1-10 R^{40} and -carbocyclyl optionally substituted with 1-12 R^{41};

R^{15} is selected from the group consisting of a single bond, H, unsubstituted —(C_{1-9} alkyl), unsubstituted —(C_{2-9} alkenyl), unsubstituted —(C_{2-9} alkynyl), unsubstituted —(C_{1-9} haloalkyl), —(C_{1-4} alkylene)OR^{42}, —(C_{1-4} alkylene)$_p$heterocyclyl optionally substituted with 1-10 R^{38}, and -carbocyclyl optionally substituted with 1-12 R^{39}; wherein —(C_{1-4} alkylene) is, optionally substituted with one or more substituents as defined anywhere herein;

R^{16} and R^{17} are independently selected from the group consisting of a single bond, H, halide, unsubstituted —(C_{1-9} alkyl), unsubstituted —(C_{2-9} alkenyl), unsubstituted —(C_{2-9} alkynyl), unsubstituted —(C_{1-9} haloalkyl), —N(R^{53})$_2$, —(C_{1-4} alkylene)$_p$OR^{42}, —(C_{1-4} alkylene)$_p$heterocyclyl optionally substituted with 1-10 R^{38}, and -carbocyclyl optionally substituted with 1-12 R^{39}; wherein each —(C_{1-4} alkylene) is, independently, optionally substituted with one or more substituents as defined anywhere herein;

alternatively, one of R^{15} and R^{16} or R^{16} and R^{17} are taken together to form a ring which is selected from the group consisting of -heterocyclyl optionally substituted with 1-10 R^{40} and -carbocyclyl optionally substituted with 1-12 R^{41};

R^{18} is selected from the group consisting of a single bond, H, unsubstituted —(C_{1-9} alkyl), unsubstituted —(C_{2-9} alkenyl), unsubstituted —(C_{2-9} alkynyl), unsubstituted —(C_{1-9} haloalkyl), —(C_{1-4} alkylene)OR^{42}, —(C_{1-4} alkylene)$_p$heterocyclyl optionally substituted with 1-10 R^{38}, and -carbocyclyl optionally substituted with 1-12 R^{39}; wherein —(C_{1-4} alkylene) is, optionally substituted with one or more substituents as defined anywhere herein;

R^{19} and R^{20} are independently selected from the group consisting of a single bond, H, halide, unsubstituted —(C_{1-9} alkyl), unsubstituted —(C_{2-9} alkenyl), unsubstituted —(C_{2-9} alkynyl), unsubstituted —(C_{1-9} haloalkyl), —N(R^{53})$_2$, —(C_{1-4} alkylene)$_p$OR^{42}, —(C_{1-4} alkylene)$_p$heterocyclyl optionally substituted with 1-10 R^{38}, and -carbocyclyl optionally substituted with 1-12 R^{39}; wherein each —(C_{1-4} alkylene) is, independently, optionally substituted with one or more substituents as defined anywhere herein;

alternatively, one of R^{18} and R^{19} or R^{18} and R^{20} are taken together to form a heterocyclyl optionally substituted with 1-10 R^{40};

R^{21} is selected from the group consisting of a single bond, H, unsubstituted —(C_{1-9} alkyl), unsubstituted —(C_{2-9} alkenyl), unsubstituted —(C_{2-9} alkynyl), unsubstituted —(C_{1-9} haloalkyl), —(C_{1-4} alkylene)OR^{42}, —(C_{1-4} alkylene)$_p$heterocyclyl optionally substituted with 1-10 R^{38}, and -carbocyclyl optionally substituted with 1-12 R^{39}; wherein —(C_{1-4} alkylene) is, optionally substituted with one or more substituents as defined anywhere herein;

R^{22} and R^{23} are independently selected from the group consisting of a single bond, H, halide, unsubstituted —(C_{1-9} alkyl), unsubstituted —(C_{2-9} alkenyl), unsubstituted —(C_{2-9} alkynyl), unsubstituted —(C_{1-9} haloalkyl), —N(R^{53})$_2$, —(C_{1-4} alkylene)$_p$OR^{42}, —(C_{1-4} alkylene)$_p$heterocyclyl optionally substituted with 1-10 R^{38}, and -carbocyclyl optionally substituted with 1-12 R^{39}; wherein each —(C_{1-4} alkylene) is, independently, optionally substituted with one or more substituents as defined anywhere herein;

alternatively, R^{22} and R^{23} are taken together to form a ring which is selected from the group consisting of -heterocyclyl optionally substituted with 1-10 R^{40} and -carbocyclyl optionally substituted with 1-12 R^{41};

R^{24}, R^{25}, and R^{26} are independently selected from the group consisting of a single bond, H, halide, unsubstituted —(C_{1-9} alkyl), unsubstituted —(C_{2-9} alkenyl), unsubstituted —(C_{2-9} alkynyl), unsubstituted —(C_{1-9} haloalkyl), —N(R^{53})$_2$, —(C_{1-4} alkylene)$_p$OR^{42}, —(C_{1-4} alkylene)$_p$het-

erocyclyl optionally substituted with 1-10 R^{38}, and -carbocyclyl optionally substituted with 1-12 R^{39}; wherein each —(C_{1-4} alkylene) is, independently, optionally substituted with one or more substituents as defined anywhere herein;

with the proviso that when R^{25} is a single bond connecting R^3 to the isoquinoline ring, R^{24} and R^{26} are not methyls;

alternatively, one of R^{24} and R^{25} or R^{25} and R^{26} are taken together to form a ring which is selected from the group consisting of -heterocyclyl optionally substituted with 1-10 R^{40} and -carbocyclyl optionally substituted with 1-12 R^{41};

R^{27}, R^{28}, and R^{29} are independently selected from the group consisting of a single bond, H, halide, unsubstituted —(C_{1-9} alkyl), unsubstituted —(C_{2-9} alkenyl), unsubstituted —(C_{2-9} alkynyl), unsubstituted —(C_{1-9} haloalkyl), —$N(R^{53})_2$, —(C_{1-4} alkylene)$_p$$OR^{42}$, —($C_{1-4}$ alkylene)$_p$heterocyclyl optionally substituted with 1-10 R^{38}, and -carbocyclyl optionally substituted with 1-12 R^{39}; wherein each —(C_{1-4} alkylene) is, independently, optionally substituted with one or more substituents as defined anywhere herein;

alternatively, R^{27} and R^{28} are taken together to form a ring which is selected from the group consisting of -heterocyclyl optionally substituted with 1-10 R^{40} and -carbocyclyl optionally substituted with 1-12 R^{41};

R^{30} and R^{31} are independently selected from the group consisting of a single bond, H, halide, unsubstituted —(C_{1-9} alkyl), unsubstituted —(C_{2-9} alkenyl), unsubstituted —(C_{2-9} alkynyl), unsubstituted —(C_{1-9} haloalkyl), —$N(R^{53})_2$, —(C_{1-4} alkylene)$_p$$OR^{42}$, —($C_{1-4}$ alkylene)$_p$heterocyclyl optionally substituted with 1-10 R^{38}, and -carbocyclyl optionally substituted with 1-12 R^{39}; wherein each —(C_{1-4} alkylene) is, independently, optionally substituted with one or more substituents as defined anywhere herein;

alternatively, R^{30} and R^{31} are taken together to form a ring which is selected from the group consisting of -heterocyclyl optionally substituted with 1-10 R^{40} and -carbocyclyl optionally substituted with 1-12 R^{41};

R^{32} and R^{33} are independently selected from the group consisting of a single bond, H, halide, unsubstituted —(C_{1-9} alkyl), unsubstituted —(C_{2-9} alkenyl), unsubstituted —(C_{2-9} alkynyl), unsubstituted —(C_{1-9} haloalkyl), —$N(R^{53})_2$, —(C_{1-4} alkylene)$_p$$OR^{42}$, —($C_{1-4}$ alkylene)$_p$heterocyclyl optionally substituted with 1-10 R^{38}, and -carbocyclyl optionally substituted with 1-12 R^{39}; wherein each —(C_{1-4} alkylene) is, independently, optionally substituted with one or more substituents as defined anywhere herein;

R^{34} and R^{35} are independently selected from the group consisting of a single bond, H, halide, unsubstituted —(C_{1-9} alkyl), unsubstituted —(C_{2-9} alkenyl), unsubstituted —(C_{2-9} alkynyl), unsubstituted —(C_{1-9} haloalkyl), —$N(R^{53})_2$, —(C_{1-4} alkylene)$_p$$OR^{42}$, —($C_{1-4}$ alkylene)$_p$heterocyclyl optionally substituted with 1-10 R^{38}, and -carbocyclyl optionally substituted with 1-12 R^{39}; wherein each —(C_{1-4} alkylene) is, independently, optionally substituted with one or more substituents as defined anywhere herein;

alternatively, R^{34} and R^{35} are taken together to form a ring which is selected from the group consisting of -heterocyclyl optionally substituted with 1-10 R^{40} and -carbocyclyl optionally substituted with 1-12 R^{41};

each R^{36} is independently selected from the group consisting of halide, unsubstituted —(C_{1-9} alkyl), unsubstituted —(C_{2-9} alkenyl), unsubstituted —(C_{2-9} alkynyl), unsubstituted —(C_{1-9} haloalkyl), —(C_{1-4} alkylene)$_p$$OR^{42}$, —($C_{1-4}$ alkylene)$_p$heterocyclyl optionally substituted with 1-10 R^{43}, —(C_{1-4} alkylene)$_p$carbocyclyl optionally substituted with 1-12 R^{44}, —C(=O)(R^{50}), —(C_{1-4} alkylene)C(=O)OR^{51}, —(C_{1-4} alkylene)aryl optionally substituted with one or more halides, —(C_{1-4} alkylene)$_p$heteroaryl optionally substituted with one or more halides, and —SO_2(R^{52}); wherein each —(C_{1-4} alkylene) is, independently, optionally substituted with one or more substituents as defined anywhere herein;

alternatively, two R^{36} attached to the same carbon atom can together represent =O to form a carbonyl group;

each R^{37} is independently selected from the group consisting of halide, unsubstituted —(C_{1-9} alkyl), unsubstituted —(C_{2-9} alkenyl), unsubstituted —(C_{2-9} alkynyl), unsubstituted —(C_{1-9} haloalkyl), —(C_{1-4} alkylene)$_p$$OR^{42}$, —$N(R^{53})_2$, —C(=O)($R^{50}$), —C(=O)$OR^{51}$, —($C_{1-4}$ alkylene)$_p$heterocyclyl optionally substituted with 1-10 R^{43}, and —(C_{1-4} alkylene)$_p$carbocyclyl optionally substituted with 1-12 R^{44}; wherein each —(C_{1-4} alkylene) is, independently, optionally substituted with one or more substituents as defined anywhere herein;

each R^{38} independently is selected from the group consisting of halide, unsubstituted —(C_{1-5} alkyl), unsubstituted —(C_{2-5} alkenyl), unsubstituted —(C_{2-5} alkynyl), unsubstituted —(C_{1-5} haloalkyl), —CN, and —(C_{1-4} alkylene)$_p$carbocyclyl optionally substituted with 1-12 R^{44}; wherein each —(C_{1-4} alkylene) is, independently, optionally substituted with one or more substituents as defined anywhere herein;

each R^{39} is independently selected from the group consisting of halide, unsubstituted —(C_{1-5} alkyl), unsubstituted —(C_{2-5} alkenyl), unsubstituted —(C_{2-5} alkynyl), unsubstituted —(C_{1-5} haloalkyl), —CN, and —(C_{1-4} alkylene)$_p$carbocyclyl optionally substituted with 1-12 R^{44}; wherein each —(C_{1-4} alkylene) is, independently, optionally substituted with one or more substituents as defined anywhere herein;

each R^{40} is independently selected from the group consisting of halide, unsubstituted —(C_{1-5} alkyl), unsubstituted —(C_{2-5} alkenyl), unsubstituted —(C_{2-5} alkynyl), unsubstituted —(C_{1-5} haloalkyl), —CN, and —(C_{1-4} alkylene)$_p$carbocyclyl optionally substituted with 1-12 R^{44}; wherein each —(C_{1-4} alkylene) is, independently, optionally substituted with one or more substituents as defined anywhere herein;

each R^{41} is independently selected from the group consisting of halide, unsubstituted —(C_{1-5} alkyl), unsubstituted —(C_{2-5} alkenyl), unsubstituted —(C_{2-5} alkynyl), unsubstituted —(C_{1-5} haloalkyl), and —CN;

each R^{42} is independently selected from the group consisting of unsubstituted —(C_{1-5} alkyl), unsubstituted —(C_{2-5} alkenyl), unsubstituted —(C_{2-5} alkynyl), unsubstituted —(C_{1-5} haloalkyl), and —(C_{1-4} alkylene)$_p$carbocyclyl optionally substituted with 1-12 R^{44}; wherein each —(C_{1-4} alkylene) is, independently, optionally substituted with one or more substituents as defined anywhere herein;

each R^{43} is independently selected from the group consisting of halide, unsubstituted —(C_{1-5} alkyl), unsubstituted —(C_{2-5} alkenyl), unsubstituted —(C_{2-5} alkynyl), unsubstituted —(C_{1-5} haloalkyl), —CN, and —(C_{1-4} alkylene)$_p$carbocyclyl optionally substituted with 1-12 R^{44}; wherein each —(C_{1-4} alkylene) is, independently, optionally substituted with one or more substituents as defined anywhere herein;

each R^{44} is independently selected from the group consisting of halide, unsubstituted —(C_{1-5} alkyl), unsubstituted —(C_{2-5} alkenyl), unsubstituted —(C_{2-5} alkynyl), unsubstituted —(C_{1-5} haloalkyl), and —CN;

R^{46} is attached to the nitrogen and is selected from the group consisting of H, unsubstituted —(C_{1-9} alkyl), unsubstituted —(C_{2-9} alkenyl), unsubstituted —(C_{2-9} alkynyl), unsubstituted —(C_{1-9} haloalkyl), —(C_{1-4} alkylene)$_p$heterocyclyl optionally substituted with 1-10 R^{38}, and -carbocyclyl optionally substituted with 1-12 R^{39}; wherein —(C_{1-4} alkylene) is, optionally substituted with one or more substituents as defined anywhere herein;

R^{47} is attached to the nitrogen and is selected from the group consisting of unsubstituted —(C_{1-9} alkyl), unsubstituted —(C_{2-9} alkenyl), unsubstituted —(C_{2-9} alkynyl), unsubstituted —(C_{1-9} haloalkyl), —(C_{1-4} alkylene)$_p$heterocyclyl optionally substituted with 1-10 R^{38}, and -carbocyclyl optionally substituted with 1-12 R^{39}; wherein —(C_{1-4} alkylene) is, optionally substituted with one or more substituents as defined anywhere herein;

R^{48} is attached to the nitrogen and selected from the group consisting of H, unsubstituted —(C_{1-5} alkyl), unsubstituted —(C_{2-5} alkenyl), unsubstituted —(C_{2-5} alkynyl), and unsubstituted —(C_{1-5} haloalkyl);

R^{49} is attached to the nitrogen and is selected from the group consisting of —(C_{1-4} alkylene)$_p$heterocyclyl optionally substituted with 1-10 R^{38}, and —(C_{1-4} alkylene)$_p$carbocyclyl optionally substituted with 1-12 R^{39}; wherein each —(C_{1-4} alkylene) is, independently, optionally substituted with one or more substituents as defined anywhere herein;

R^{50} is selected from the group consisting of H, unsubstituted —(C_{3-5} alkyl), unsubstituted —(C_{2-5} alkenyl), unsubstituted —(C_{2-5} alkynyl), unsubstituted —(C_{1-5} haloalkyl), —(C_{1-4} alkylene)$_p$aryl optionally substituted with one or more halides or unsubstituted —(C_{1-5} alkyl), —(C_{1-4} alkylene)$_p$heteroaryl optionally substituted with one or more halides or unsubstituted —(C_{1-5} alkyl), and —(C_{1-4} alkylene)$_p$heterocyclyl optionally substituted with one or more halides or one or more unsubstituted —(C_{1-5} alkyl); wherein each —(C_{1-4} alkylene) is, independently, optionally substituted with one or more substituents as defined anywhere herein;

R^{51} is selected from the group consisting of H, unsubstituted —(C_{1-5} alkyl), unsubstituted —(C_{2-5} alkenyl), unsubstituted —(C_{2-5} alkynyl), unsubstituted —(C_{1-5} haloalkyl), —(C_{1-4} alkylene)$_p$aryl optionally substituted with one or more halides or unsubstituted —(C_{1-5} alkyl), —(C_{1-4} alkylene)$_p$heteroaryl optionally substituted with one or more halides or unsubstituted —(C_{1-5} alkyl), and —(C_{1-4} alkylene)$_p$heterocyclyl optionally substituted with one or more halides or one or more unsubstituted —(C_{1-5} alkyl); wherein each —(C_{1-4} alkylene) is, independently, optionally substituted with one or more substituents as defined anywhere herein;

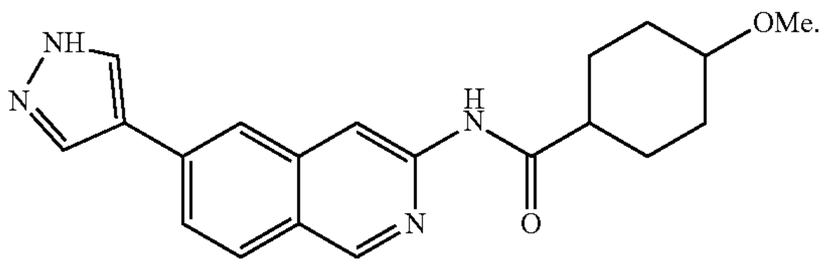
R^{52} is selected from the group consisting of unsubstituted —(C_{1-5} alkyl), unsubstituted —(C_{2-5} alkenyl), unsubstituted —(C_{2-5} alkynyl), unsubstituted —(C_{1-5} haloalkyl), —(C_{1-4} alkylene)$_p$aryl optionally substituted with one or more halides or unsubstituted —(C_{1-5} alkyl), —(C_{1-4} alkylene)$_p$ heteroaryl optionally substituted with one or more halides or unsubstituted —(C_{1-5} alkyl), and —(C_{1-4} alkylene)$_p$heterocyclyl optionally substituted with one or more halides or one or more unsubstituted —(C_{1-5} alkyl); wherein —(C_{1-4} alkylene) is, optionally substituted with one or more substituents as defined anywhere herein;

each R^{53} is independently selected from the group consisting of H, unsubstituted —(C_{1-5} alkyl), unsubstituted —(C_{2-5} alkenyl), and unsubstituted —(C_{2-5}alkynyl);

each X is O or S; and

each p is independently 0 or 1; and

with the proviso that Formula I is not a structure selected from the group consisting of:



Some embodiments include stereoisomers and pharmaceutically acceptable salts of a compound of Formula (I). Some embodiments include pharmaceutically acceptable salts of a compound of Formula (I).

Some embodiments include pro-drugs of a compound of Formula (I).

Some embodiments of the present disclosure include pharmaceutical compositions comprising a compound of Formula (I) and a pharmaceutically acceptable carrier, diluent, or excipient.

Other embodiments disclosed herein include methods of inhibiting one or more members of the Wnt pathway, including one or more Wnt proteins by administering to a patient affected by a disorder or disease in which aberrant Wnt signaling is implicated, such as cancer and other diseases associated with abnormal angiogenesis, cellular proliferation, cell cycling and mutations in Wnt signaling components, a compound according to Formula (I). Accordingly, the compounds and compositions provided herein can be used to treat cancer, to reduce or inhibit angiogenesis, to reduce or inhibit cellular proliferation and correct a genetic disorder due to mutations in Wnt signaling components.

Other embodiments disclosed herein include methods of inhibiting DYRK1A by administering to a patient affected by a disorder or disease in which DYRK1A overexpression is implicated, such as Alzheimer's Disease, Amyotrophic Lateral Sclerosis, Down Syndrome, Frontotemporal Dementia with Parkinsonism-17 (FTDP-17), Lewy body dementia, Parkinson's Disease, Pick's Disease, and additional diseases with pronounced neurodegeneration such as Autism, Dementia, Epilepsy, Huntington's Disease, Multiple Sclerosis; diseases and disorders associated with acquired brain injury such as Chronic Traumatic Encephalopathy, Traumatic Brain Injury, Tumor and Stroke.

Non-limiting examples of diseases which can be treated with the compounds and compositions provided herein include a variety of cancers, diabetic retinopathy, pulmonary fibrosis, rheumatoid arthritis, sepsis, ankylosing spondylitis, psoriasis, scleroderma, mycotic and viral infections, osteochondrodysplasia, Alzheimer's disease, lung disease, bone/osteoporotic (wrist, spine, shoulder and hip) fractures, articular cartilage (chondral) defects, degenerative disc disease (or intervertebral disc degeneration), polyposis coli, osteoporosis-pseudoglioma syndrome, familial exudative vitreoretinopathy, retinal angiogenesis, early coronary disease, tetra-amelia syndrome, Müllerian-duct regression and virilization, SERKAL syndrome, diabetes mellitus type 2, Fuhrmann syndrome, Al-Awadi/Raas-Rothschild/Schinzel phocomelia syndrome, odonto-onycho-dermal dysplasia, obesity, split-hand/foot malformation, caudal duplication syndrome, tooth agenesis, Wilms tumor, skeletal dysplasia, focal dermal hypoplasia, autosomal recessive anonychia, neural tube defects, alpha-thalassemia (ATRX) syndrome, fragile X syndrome, ICF syndrome, Angelman syndrome, Prader-Willi syndrome, Beckwith-Wiedemann Syndrome, Norrie disease, and Rett syndrome.

Some embodiments of the present disclosure include methods to prepare compounds of Formula (I).

It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of the disclosure, as claimed.

DETAILED DESCRIPTION

Provided herein are compositions and methods for inhibiting one or more members of the Wnt pathway, including

one or more Wnt proteins. Other Wnt inhibitors and methods for using the same are disclosed in U.S. application Ser. Nos. 13/614,296; 14/019,229; and 14/664,517, all of which are incorporated by reference in their entirety herein.

Provided herein are compositions and methods for inhibiting DYRK1A. Other DYRK1A inhibitors and methods for using the same are disclosed in U.S. application Ser. No. 14/664,517, which is incorporated by reference in its entirety herein.

Some embodiments provided herein relate to a method for treating a disease including, but not limited to, neurological diseases or disorders, cancers, chronic inflammation, diabetic retinopathy, pulmonary fibrosis, rheumatoid arthritis, sepsis, ankylosing spondylitis, psoriasis, scleroderma, mycotic and viral infections, bone and cartilage diseases, lung disease, osteoarthritis, articular cartilage (chondral) defects, degenerative disc disease (or intervertebral disc degeneration), polyposis coli, bone density and vascular defects in the eye (Osteoporosis-pseudoglioma Syndrome, OPPG), familial exudative vitreoretinopathy, retinal angiogenesis, early coronary disease, tetra-amelia, Müllerian-duct regression and virilization, SERKAL syndrome, type II diabetes, Fuhrmann syndrome, Al-Awadi/Raas-Rothschild/Schinzel phocomelia syndrome, odonto-onycho-dermal dysplasia, obesity, split-hand/foot malformation, caudal duplication, tooth agenesis, Wilms tumor, skeletal dysplasia, focal dermal hypoplasia, autosomal recessive anonychia, neural tube defects, alpha-thalassemia (ATRX) syndrome, fragile X syndrome, ICF syndrome, Angelman's syndrome, Prader-Willi syndrome, Beckwith-Wiedemann Syndrome, Norrie disease, and Rett syndrome.

In some embodiments, non-limiting examples of bone and cartilage diseases which can be treated with the compounds and compositions provided herein include bone spur (osteophytes), craniosynostosis, fibrodysplasia ossificans progressive, fibrous dysplasia, giant cell tumor of bone, hip labral tear, meniscal tears, osteoarthritis, articular cartilage (chondral) defects, degenerative disc disease (or intervertebral disc degeneration), osteochondritis dissecans, osteochondroma (bone tumor), osteopetrosis, relapsing polychondritis, and Salter-Harris fractures.

In some embodiments, non-limiting examples of a neurological disease or disorder associated with tau protein, amyloid or alpha-synuclein pathology which can be treated with the compounds and compositions provided herein include, but are not limited to, Alzheimer's Disease, Amyotrophic Lateral Sclerosis, Down Syndrome, Frontotemporal Dementia with Parkinsonism-17 (FTDP-17), Lewy body dementia, Parkinson's Disease, Pick's Disease, and additional diseases with pronounced neurodegeneration such as Autism, Dementia, Epilepsy, Huntington's Disease, Multiple Sclerosis; diseases and disorders associated with acquired brain injury such as Chronic Traumatic Encephalopathy, Traumatic Brain Injury, Tumor, and Stroke.

In some embodiments, non-limiting examples of diseases in which chronic inflammation is involved which can be treated with the compounds and compositions provided herein include eye disorders, joint pain, arthritis (rheumatoid, osteo, psoriatic gout), cancers (colon, breast, lung, pancreas, and others), gastrointestinal disorders (ulcerative colitis and inflammatory bowel diseases), pulmonary disorders (chronic obstructive pulmonary disorder and asthma), allergies, skin disorders (atopic dermatitis and psoriasis), diabetes, pancreatitis, tendonitis, hepatitis, heart disease, myocarditis, stroke, lupus, and neurological disorders such as multiple sclerosis, Parkinson's and dementia including Alzheimer's disease.

In some embodiments, non-limiting examples of cancers which can be treated with the compounds and compositions provided herein include colon, ovarian, pancreatic, breast, liver, prostate, and hematologic cancers.

In some embodiments, pharmaceutical compositions are provided that are effective for treatment of a disease of an animal, e.g., a mammal, caused by either the pathological activation or mutations of the Wnt pathway or DYRK1A overexpression. The composition includes a pharmaceutically acceptable carrier and a compound as described herein.

Definitions

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of ordinary skill in the art to which this disclosure belongs. All patents, applications, published applications, and other publications are incorporated by reference in their entirety. In the event that there is a plurality of definitions for a term herein, those in this section prevail unless stated otherwise.

As used herein, "alkyl" means a branched, or straight chain chemical group containing only carbon and hydrogen, such as methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, n-pentyl, iso-pentyl, sec-pentyl and neo-pentyl. Alkyl groups can either be unsubstituted or substituted with one or more substituents. In some embodiments, alkyl groups include 1 to 9 carbon atoms (for example, 1 to 6 carbon atoms, 1 to 4 carbon atoms, or 1 to 2 carbon atoms).

As used herein, "alkenyl" means a straight or branched chain chemical group containing only carbon and hydrogen and containing at least one carbon-carbon double bond, such as ethenyl, 1-propenyl, 2-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl, and the like. In various embodiments, alkenyl groups can either be unsubstituted or substituted with one or more substituents. Typically, alkenyl groups will comprise 2 to 9 carbon atoms (for example, 2 to 6 carbon atoms, 2 to 4 carbon atoms, or 2 carbon atoms).

As used herein, "alkynyl" means a straight or branched chain chemical group containing only carbon and hydrogen and containing at least one carbon-carbon triple bond, such as ethynyl, 1-propynyl, 1-butynyl, 2-butynyl, and the like. In various embodiments, alkynyl groups can either be unsubstituted or substituted with one or more substituents. Typically, alkynyl groups will comprise 2 to 9 carbon atoms (for example, 2 to 6 carbon atoms, 2 to 4 carbon atoms, or 2 carbon atoms).

As used herein, "alkylene" means a bivalent branched, or straight chain chemical group containing only carbon and hydrogen, such as methylene, ethylene, n-propylene, iso-propylene, n-butylene, iso-butylene, sec-butylene, tert-butylene, n-pentylene, iso-pentylene, sec-pentylene and neo-pentylene. Alkylene groups can either be unsubstituted or substituted with one or more substituents. In some embodiments, alkylene groups include 1 to 9 carbon atoms (for example, 1 to 6 carbon atoms, 1 to 4 carbon atoms, or 1 to 2 carbon atoms).

As used herein, "alkenylene" means a bivalent branched, or straight chain chemical group containing only carbon and hydrogen and containing at least one carbon-carbon double bond, such as ethenylene, 1-propenylene, 2-propenylene, 2-methyl-1-propenylene, 1-butenylene, 2-butenylene, and the like. In various embodiments, alkenylene groups can either be unsubstituted or substituted with one or more substituents. Typically, alkenylene groups will comprise 2 to

9 carbon atoms (for example, 2 to 6 carbon atoms, 2 to 4 carbon atoms, or 2 carbon atoms).

As used herein, "alkynylene" means a bivalent branched, or straight chain chemical group containing only carbon and hydrogen and containing at least one carbon-carbon triple bond, such as ethynylene, 1-propynylene, 1-butynylene, 2-butynylene, and the like. In various embodiments, alkynylene groups can either be unsubstituted or substituted with one or more substituents. Typically, alkynylene groups will comprise 2 to 9 carbon atoms (for example, 2 to 6 carbon atoms, 2 to 4 carbon atoms, or 2 carbon atoms).

As used herein, "alkoxy" means an alkyl-O— group in which the alkyl group is as described herein. Exemplary alkoxy groups include methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, s-butoxy, t-butoxy, pentoxy, hexoxy and heptoxy, and also the linear or branched positional isomers thereof.

As used herein, "haloalkoxy" means a haloalkyl-O— group in which the haloalkyl group is as described herein. Exemplary haloalkoxy groups include fluoromethoxy, difluoromethoxy, trifluoromethoxy, and also the linear or branched positional isomers thereof.

As used herein, "carbocyclyl" means a cyclic ring system containing only carbon atoms in the ring system backbone, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cyclohexenyl. Carbocyclyls may include multiple fused rings. Carbocyclyls may have any degree of saturation provided that none of the rings in the ring system are aromatic. Carbocyclyl groups can either be unsubstituted or substituted with one or more substituents. In some embodiments, carbocyclyl groups include 3 to 10 carbon atoms, for example, 3 to 6 carbon atoms.

As used herein, "aryl" means a mono-, bi-, tri- or polycyclic group with only carbon atoms present in the ring backbone having 5 to 14 ring atoms, alternatively 5, 6, 9, or 10 ring atoms; and having 6, 10, or 14 pi electrons shared in a cyclic array; wherein at least one ring in the system is aromatic. Aryl groups can either be unsubstituted or substituted with one or more substituents. Examples of aryl include phenyl, naphthyl, tetrahydronaphthyl, 2,3-dihydro-1H-indenyl, and others. In some embodiments, the aryl is phenyl.

As used herein, "arylalkylene" means an aryl-alkylene-group in which the aryl and alkylene moieties are as previously described. In some embodiments, arylalkylene groups contain a C_{1-4}alkylene moiety. Exemplary arylalkylene groups include benzyl and 2-phenethyl.

As used herein, the term "heteroaryl" means a mono-, bi-, tri- or polycyclic group having 5 to 14 ring atoms, alternatively 5, 6, 9, or 10 ring atoms; and having 6, 10, or 14 pi electrons shared in a cyclic array; wherein at least one ring in the system is aromatic, and at least one ring in the system contains one or more heteroatoms independently selected from the group consisting of N, O, and S. Heteroaryl groups can either be unsubstituted or substituted with one or more substituents. Examples of heteroaryl include thienyl, pyridinyl, furyl, oxazolyl, oxadiazolyl, pyrrolyl, imidazolyl, triazolyl, thiodiazolyl, pyrazolyl, isoxazolyl, thiadiazolyl, pyranyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazinyl, thiazolyl benzothienyl, benzoxadiazolyl, benzofuranyl, benzimidazolyl, benzotriazolyl, cinnolinyl, indazolyl, indolyl, isoquinolinyl, isothiazolyl, naphthyridinyl, purinyl, thienopyridinyl, pyrido[2,3-d]pyrimidinyl, pyrrolo[2,3-b]pyridinyl, quinazolinyl, quinolinyl, thieno[2,3-c]pyridinyl, pyrazolo[3,4-b]pyridinyl, pyrazolo[3,4-c]pyridinyl, pyrazolo[4,3-c]pyridine, pyrazolo[4,3-b]pyridinyl, tetrazolyl, chromane, 2,3-dihydrobenzo[b][1,4]dioxine, benzo[d][1,3]dioxole, 2,3-dihydrobenzofuran, tetrahydroquinoline, 2,3-dihydrobenzo[b][1,4]oxathiine, isoindoline, and others. In some embodiments, the heteroaryl is selected from thienyl, pyridinyl, furyl, pyrazolyl, imidazolyl, isoindolinyl, pyranyl, pyrazinyl, and pyrimidinyl.

As used herein, "halo", "halide" or "halogen" is a chloro, bromo, fluoro, or iodo atom radical. In some embodiments, a halo is a chloro, bromo or fluoro. For example, a halide can be fluoro.

As used herein, "haloalkyl" means a hydrocarbon substituent, which is a linear or branched, alkyl, alkenyl or alkynyl substituted with one or more chloro, bromo, fluoro, and/or iodo atom(s). In some embodiments, a haloalkyl is a fluoroalkyls, wherein one or more of the hydrogen atoms have been substituted by fluoro. In some embodiments, haloalkyls are of 1 to about 3 carbons in length (e.g., 1 to about 2 carbons in length or 1 carbon in length). The term "haloalkylene" means a diradical variant of haloalkyl, and such diradicals may act as spacers between radicals, other atoms, or between a ring and another functional group.

As used herein, "heterocyclyl" means a nonaromatic cyclic ring system comprising at least one heteroatom in the ring system backbone. Heterocyclyls may include multiple fused rings. Heterocyclyls may be substituted or unsubstituted with one or more substituents. In some embodiments, heterocycles have 3-11 members. In six membered monocyclic heterocycles, the heteroatom(s) are selected from one to three of O, N or S, and wherein when the heterocycle is five membered, it can have one or two heteroatoms selected from O, N, or S. Examples of heterocyclyl include azirinyl, aziridinyl, azetidinyl, oxetanyl, thietanyl, 1,4,2-dithiazolyl, dihydropyridinyl, 1,3-dioxanyl, 1,4-dioxanyl, 1,3-dioxolanyl, morpholinyl, thiomorpholinyl, piperazinyl, pyranyl, pyrrolidinyl, tetrahydrofuryl, tetrahydropyridinyl, oxazinyl, thiazinyl, thiinyl, thiazolidinyl, isothiazolidinyl, oxazolidinyl, isoxazolidinyl, piperidinyl, pyrazolidinyl imidazolidinyl, thiomorpholinyl, and others. In some embodiments, the heterocyclyl is selected from azetidinyl, morpholinyl, piperazinyl, pyrrolidinyl, and tetrahydropyridinyl.

As used herein, "monocyclic heterocyclyl" means a single nonaromatic cyclic ring comprising at least one heteroatom in the ring system backbone. Heterocyclyls may be substituted or unsubstituted with one or more substituents. In some embodiments, heterocycles have 3-7 members. In six membered monocyclic heterocycles, the heteroatom(s) are selected from one to three of O, N or S, and wherein when the heterocycle is five membered, it can have one or two heteroatoms selected from O, N, or S. Examples of heterocyclyls include azirinyl, aziridinyl, azetidinyl, oxetanyl, thietanyl, 1,4,2-dithiazolyl, dihydropyridinyl, 1,3-dioxanyl, 1,4-dioxanyl, 1,3-dioxolanyl, morpholinyl, thiomorpholinyl, piperazinyl, pyranyl, pyrrolidinyl, tetrahydrofuryl, tetrahydropyridinyl, oxazinyl, thiazinyl, thiinyl, thiazolidinyl, isothiazolidinyl, oxazolidinyl, isoxazolidinyl, piperidinyl, pyrazolidinyl imidazolidinyl, thiomorpholinyl, and others.

As used herein, "bicyclic heterocyclyl" means a nonaromatic bicyclic ring system comprising at least one heteroatom in the ring system backbone. Bicyclic heterocyclyls may be substituted or unsubstituted with one or more substituents. In some embodiments, bicyclic heterocycles have 4-11 members with the heteroatom(s) being selected from one to five of O, N or S. Examples of bicyclic heterocyclyls include 2-azabicyclo[1.1.0]butane, 2-azabicyclo[2.1.0]pentane, 2-azabicyclo[1.1.1]pentane, 3-azabicyclo[3.1.0]hexane, 5-azabicyclo[2.1.1]hexane, 3-azabicyclo[3.2.0]heptane, octahydrocyclopenta[c]pyrrole, 3-azabicyclo[4.1.0]heptane, 7-azabicyclo[2.2.1]heptane,

6-azabicyclo[3.1.1]heptane, 7-azabicyclo[4.2.0]octane, 2-azabicyclo[2.2.2]octane, and the like.

As used herein, "spirocyclic heterocyclyl" means a non-aromatic bicyclic ring system comprising at least one heteroatom in the ring system backbone and with the rings connected through just one atom. Spirocyclic heterocyclyls may be substituted or unsubstituted with one or more substituents. In some embodiments, spirocyclic heterocycles have 5-11 members with the heteroatom(s) being selected from one to five of O, N or S. Examples of spirocyclic heterocyclyls include 2-azaspiro[2.2]pentane, 4-azaspiro[2.5]octane, 1-azaspiro[3.5]nonane, 2-azaspiro[3.5]nonane, 7-azaspiro[3.5]nonane, 2-azaspiro[4.4]nonane, 6-azaspiro[2.6]nonane, 1,7-diazaspiro[4.5]decane, 2,5-diazaspiro[3.6]decane, and the like.

The term "substituted" refers to moieties having substituents replacing a hydrogen on one or more non-hydrogen atoms of the molecule. It will be understood that "substitution" or "substituted with" includes the implicit proviso that such substitution is in accordance with permitted valence of the substituted atom and the substituent, and that the substitution results in a stable compound, e.g., which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, etc. Substituents can include, for example, —(C_{1-9} alkyl) optionally substituted with one or more of hydroxyl, —NH_2, —NH(C_{1-3} alkyl), and —N(C_{1-3} alkyl)$_2$; —(C_{1-9} haloalkyl); a halide; a hydroxyl; a carbonyl [such as —C(O)OR, and —C(O)R]; a thiocarbonyl [such as —C(S)OR, —C(O)SR, and —C(S)R]; (C_{1-9} alkoxy) optionally substituted with one or more of halide, hydroxyl, —NH_2, —NH(C_{1-3} alkyl), and —N(C_{1-3} alkyl)$_2$; —$OPO(OH)_2$; a phosphonate [such as —$PO(OH)_2$ and —$PO(OR')_2$]; —OPO(OR')R"; —NRR'; —C(O)NRR'; —C(NR)NR'R"; —C(NR')R"; a cyano; a nitro; an azido; —SH; —S—R; —OSO_2(OR); a sulfonate [such as —SO_2(OH) and —SO_2(OR)]; —SO_2NR'R"; and —SO_2R; in which each occurrence of R, R' and R" are independently selected from H; —(C_{1-9} alkyl); C_{6-10} aryl optionally substituted with from 1-3R'"; 5-10 membered heteroaryl having from 1-4 heteroatoms independently selected from N, O, and S and optionally substituted with from 1-3 R'"; C_{3-7} carbocyclyl optionally substituted with from 1-3 R'"; and 3-8 membered heterocyclyl having from 1-4 heteroatoms independently selected from N, O, and S and optionally substituted with from 1-3 R'"; wherein each R'" is independently selected from —(C_{1-6} alkyl), —(C_{1-6} haloalkyl), a halide (e.g., F), a hydroxyl, —C(O)OR, —C(O)R, —(C_{1-6} alkoxyl), —NRR', —C(O)NRR', and a cyano, in which each occurrence of R and R' is independently selected from H and —(C_{1-6} alkyl). In some embodiments, the substituent is selected from —(C_{1-6} alkyl), —(C_{1-6} haloalkyl), a halide (e.g., F), a hydroxyl, —C(O)OR, —C(O)R, —(C_{1-6} alkoxyl), —NRR', —C(O)NRR', and a cyano, in which each occurrence of R and R' is independently selected from H and —(C_{1-6} alkyl).

As used herein, when two groups are indicated to be "linked" or "bonded" to form a "ring", it is to be understood that a bond is formed between the two groups and may involve replacement of a hydrogen atom on one or both groups with the bond, thereby forming a carbocyclyl, heterocyclyl, aryl, or heteroaryl ring. The skilled artisan will recognize that such rings can and are readily formed by routine chemical reactions. In some embodiments, such rings have from 3-7 members, for example, 5 or 6 members.

The skilled artisan will recognize that some chemical structures described herein may be represented on paper by one or more other resonance forms; or may exist in one or more other tautomeric forms, even when kinetically, the artisan recognizes that such tautomeric forms represent only a very small portion of a sample of such compound(s). Such compounds are clearly contemplated within the scope of this disclosure, though such resonance forms or tautomers are not explicitly represented herein.

The compounds provided herein may encompass various stereochemical forms. The compounds also encompass diastereomers as well as optical isomers, e.g., mixtures of enantiomers including racemic mixtures, as well as individual enantiomers and diastereomers, which arise as a consequence of structural asymmetry in certain compounds. Separation of the individual isomers or selective synthesis of the individual isomers is accomplished by application of various methods which are well known to practitioners in the art. Unless otherwise indicated, when a disclosed compound is named or depicted by a structure without specifying the stereochemistry and has one or more chiral centers, it is understood to represent all possible stereoisomers of the compound.

The present disclosure includes all pharmaceutically acceptable isotopically labeled compounds of Formula I wherein one or more atoms are replaced by atoms having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number which predominates in nature. Examples of isotopes suitable for inclusion in the compounds of the disclosure include, but are not limited to, isotopes of hydrogen, such as ^{2}H (deuterium) and ^{3}H (tritium), carbon, such as ^{11}C, ^{13}C and ^{14}C, chlorine, such as ^{36}Cl, fluorine, such as ^{18}F, iodine, such as ^{123}I and ^{125}I, nitrogen, such as ^{13}N and ^{15}N, oxygen, such as ^{15}O, ^{17}O and ^{18}O, phosphorus, such as ^{32}P, and sulfur, such as ^{35}S.

The term "administration" or "administering" refers to a method of providing a dosage of a compound or pharmaceutical composition to a vertebrate or invertebrate, including a mammal, a bird, a fish, or an amphibian, where the method is, e.g., orally, subcutaneously, intravenously, intralymphatic, intranasally, topically, transdermally, intraperitoneally, intramuscularly, intrapulmonarilly, vaginally, rectally, ontologically, neuro-otologically, intraocularly, subconjuctivally, via anterior eye chamber injection, intravitreally, intraperitoneally, intrathecally, intracystically, intrapleurally, via wound irrigation, intrabuccally, intraabdominally, intra-articularly, intra-aurally, intrabronchially, intracapsularly, intrameningeally, via inhalation, via endotracheal or endobronchial instillation, via direct instillation into pulmonary cavities, intraspinally, intrasynovially, intrathoracically, via thoracostomy irrigation, epidurally, intratympanically, intracisternally, intravascularly, intraventricularly, intraosseously, via irrigation of infected bone, or via application as part of any admixture with a prosthetic device. The method of administration can vary depending on various factors, e.g., the components of the pharmaceutical composition, the site of the disease, the disease involved, and the severity of the disease.

A "diagnostic" as used herein is a compound, method, system, or device that assists in the identification or characterization of a health or disease state. The diagnostic can be used in standard assays as is known in the art.

The term "mammal" is used in its usual biological sense. Thus, it specifically includes humans, cattle, horses, monkeys, dogs, cats, mice, rats, cows, sheep, pigs, goats, and non-human primates, but also includes many other species.

The term "pharmaceutically acceptable carrier", "pharmaceutically acceptable diluent" or "pharmaceutically acceptable excipient" includes any and all solvents, co-solvents, complexing agents, dispersion media, coatings,

isotonic and absorption delaying agents and the like which are not biologically or otherwise undesirable. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active ingredient, its use in the therapeutic compositions is contemplated. Supplementary active ingredients can also be incorporated into the compositions. In addition, various adjuvants such as are commonly used in the art may be included. These and other such compounds are described in the literature, e.g., in the Merck Index, Merck & Company, Rahway, N.J. Considerations for the inclusion of various components in pharmaceutical compositions are described, e.g., in Gilman et al. (Eds.) (2010); *Goodman and Gilman's: The Pharmacological Basis of Therapeutics,* 12*th Ed*., The McGraw-Hill Companies.

The term "pharmaceutically acceptable salt" refers to salts that retain the biological effectiveness and properties of the compounds provided herein and, which are not biologically or otherwise undesirable. In many cases, the compounds provided herein are capable of forming acid and/or base salts by virtue of the presence of amino and/or carboxyl groups or groups similar thereto. Many such salts are known in the art, for example, as described in WO 87/05297. Pharmaceutically acceptable acid addition salts can be formed with inorganic acids and organic acids. Inorganic acids from which salts can be derived include, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like. Organic acids from which salts can be derived include, for example, acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, and the like. Pharmaceutically acceptable base addition salts can be formed with inorganic and organic bases. Inorganic bases from which salts can be derived include, for example, sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum, and the like; particularly preferred are the ammonium, potassium, sodium, calcium, and magnesium salts. Organic bases from which salts can be derived include, for example, primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, basic ion exchange resins, and the like, specifically such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, and ethanolamine.

"Patient" as used herein, means a human or a non-human mammal, e.g., a dog, a cat, a mouse, a rat, a cow, a sheep, a pig, a goat, a non-human primate, or a bird, e.g., a chicken, as well as any other vertebrate or invertebrate. In some embodiments, the patient is a human.

A "therapeutically effective amount" of a compound as provided herein is one which is sufficient to achieve the desired physiological effect and may vary according to the nature and severity of the disease condition, and the potency of the compound. "Therapeutically effective amount" is also intended to include one or more of the compounds of Formula I in combination with one or more other agents that are effective to treat the diseases and/or conditions described herein. The combination of compounds can be a synergistic combination. Synergy, as described, for example, by Chou and Talalay, *Advances in Enzyme Regulation* (1984), 22, 27-55, occurs when the effect of the compounds when administered in combination is greater than the additive effect of the compounds when administered alone as a single agent. In general, a synergistic effect is most clearly demonstrated at sub-optimal concentrations of the compounds. It will be appreciated that different concentrations may be employed for prophylaxis than for treatment of an active disease. This amount can further depend upon the patient's height, weight, sex, age and medical history.

A therapeutic effect relieves, to some extent, one or more of the symptoms of the disease.

"Treat," "treatment," or "treating," as used herein refers to administering a compound or pharmaceutical composition as provided herein for therapeutic purposes. The term "therapeutic treatment" refers to administering treatment to a patient already suffering from a disease thus causing a therapeutically beneficial effect, such as ameliorating existing symptoms, ameliorating the underlying metabolic causes of symptoms, postponing or preventing the further development of a disorder, and/or reducing the severity of symptoms that will or are expected to develop.

"Drug-eluting" and/or controlled release as used herein refers to any and all mechanisms, e.g., diffusion, migration, permeation, and/or desorption by which the drug(s) incorporated in the drug-eluting material pass therefrom over time into the surrounding body tissue.

"Drug-eluting material" and/or controlled release material as used herein refers to any natural, synthetic or semi-synthetic material capable of acquiring and retaining a desired shape or configuration and into which one or more drugs can be incorporated and from which incorporated drug(s) are capable of eluting over time.

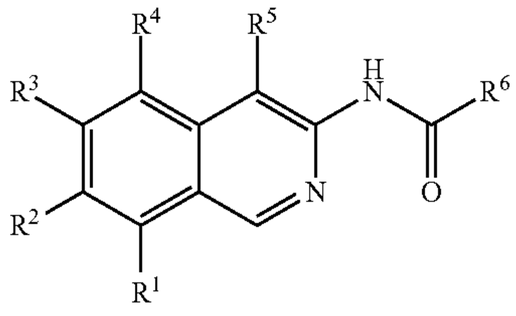
"Elutable drug" as used herein refers to any drug or combination of drugs having the ability to pass over time from the drug-eluting material in which it is incorporated into the surrounding areas of the body.

Compounds

The compounds and compositions described herein can be used as anti-proliferative agents, e.g., anti-cancer and anti-angiogenesis agents, and/or as inhibitors of the Wnt signaling pathway, e.g., for treating diseases or disorders associated with aberrant Wnt signaling. In addition, the compounds can be used as inhibitors of one or more kinases, kinase receptors, or kinase complexes. Such compounds and compositions are also useful for controlling cellular proliferation, differentiation, and/or apoptosis.

The compounds and compositions described herein can be used to inhibit DYRK1A for treating a disorder or disease in which DYRK1A overexpression is implicated, such as Alzheimer's Disease, Amyotrophic Lateral Sclerosis, Down Syndrome, Frontotemporal Dementia with Parkinsonism-17 (FTDP-17), Lewy body dementia, Parkinson's Disease, Pick's Disease, and additional diseases with pronounced neurodegeneration such as Autism, Dementia, Epilepsy, Huntington's Disease, Multiple Sclerosis; diseases and disorders associated with acquired brain injury such as Chronic Traumatic Encephalopathy, Traumatic Brain Injury, Tumor, and Stroke.

Some embodiments of the present disclosure include compounds of Formula I:



I

or salts, pharmaceutically acceptable salts, or prodrugs thereof.

In some embodiments, R^1, R^2, R^4, and R^5 are independently selected from the group consisting of H, halide, unsubstituted —(C_{1-3}haloalkyl), and unsubstituted —(C_{1-3} alkyl);

In some embodiments, R^1, R^2, R^4, and R^5 are independently selected from the group consisting of H and halide.

In some embodiments, R^1, R^2, R^4, and R^5 are independently selected from the group consisting of H and F.

In some embodiments, R^1, R^2, R^4, and R^5 are all H.

In some embodiments, R^1 is F, and R^2, R^4, and R^5 are all H.

In some embodiments, R^2 is F, and R^1, R^4, and R^5 are all H.

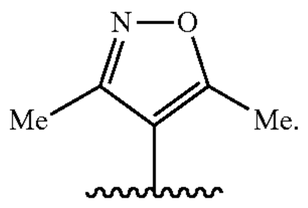
In some embodiments, R^4 is F, and R^1, R^2, and R^5 are all H.

In some embodiments, R^5 is F, and R^1, R^2, and R^4 are all H.

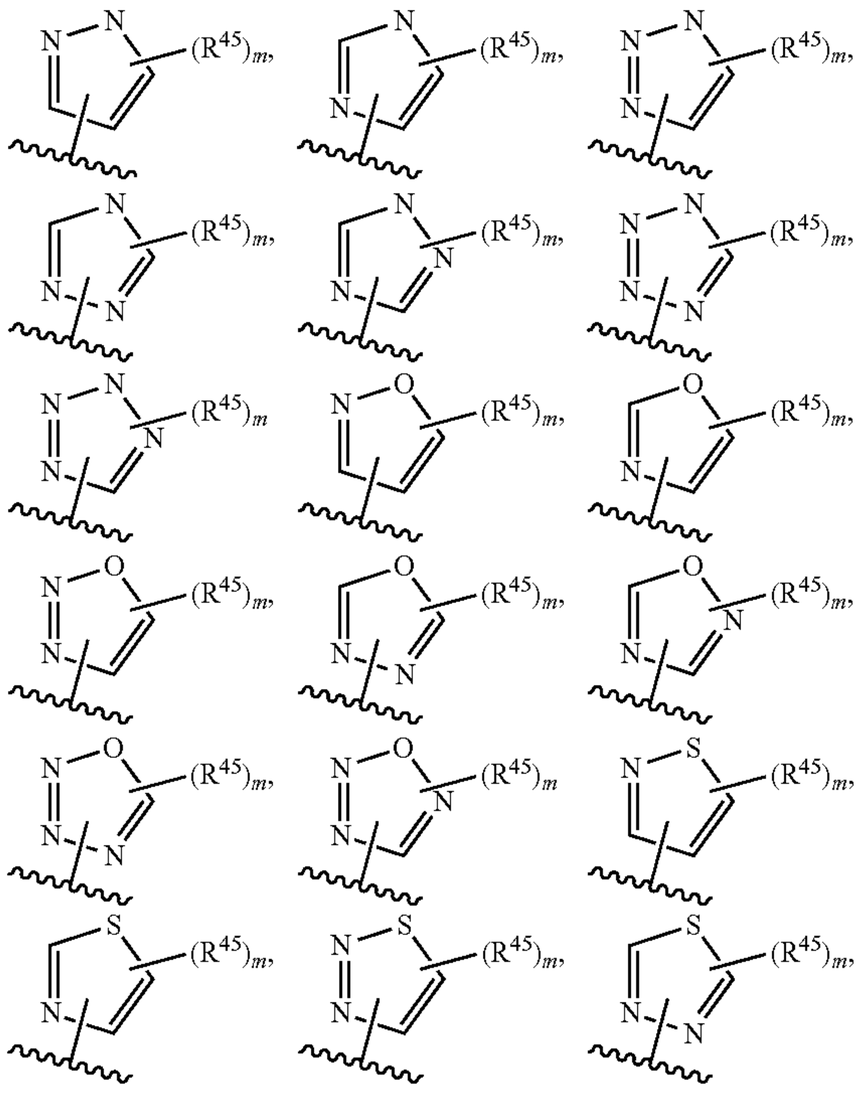
In some embodiments, R^3 is a 5-membered heteroaryl ring optionally substituted as defined anywhere herein.

In some embodiments, R^3 is 5-membered heteroaryl ring optionally substituted with 1-4 (e.g., 1-3, 1-2, 1) R^{45};

In some embodiments, there is the proviso that R^3 is not



In some embodiments, R^3 is selected from the group consisting of: furanyl optionally substituted with 1-4 (e.g., 1-3, 1-2, 1) R^{45}, thiophenyl optionally substituted with 1-4 (e.g., 1-3, 1-2, 1) R^{45}, pyrrolyl optionally substituted with 1-4 (e.g., 1-3, 1-2, 1) R^{45},



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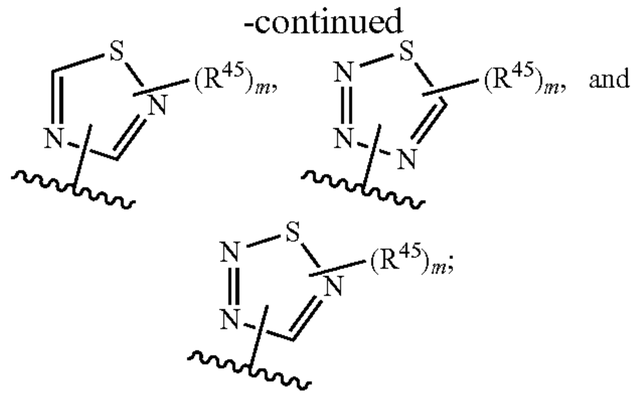
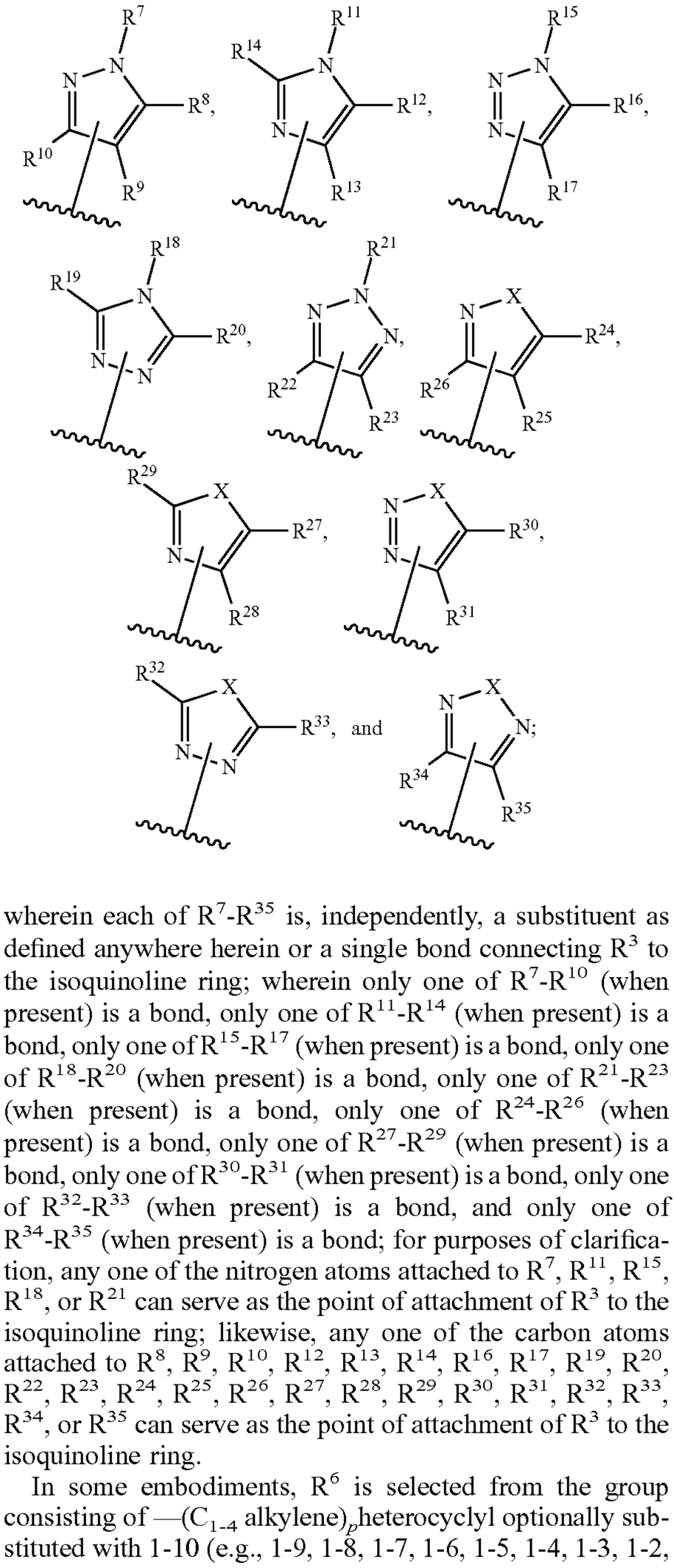


wherein each m is independently 1 to 4 (e.g., 1-3, 1-2, 1).

In some embodiments, R^3 is selected from the group consisting of:



wherein each of R^7-R^{35} is, independently, a substituent as defined anywhere herein or a single bond connecting R^3 to the isoquinoline ring; wherein only one of R^7-R^{10} (when present) is a bond, only one of R^{11}-R^{14} (when present) is a bond, only one of R^{15}-R^{17} (when present) is a bond, only one of R^{18}-R^{20} (when present) is a bond, only one of R^{21}-R^{23} (when present) is a bond, only one of R^{24}-R^{26} (when present) is a bond, only one of R^{27}-R^{29} (when present) is a bond, only one of R^{30}-R^{31} (when present) is a bond, only one of R^{32}-R^{33} (when present) is a bond, and only one of R^{34}-R^{35} (when present) is a bond; for purposes of clarification, any one of the nitrogen atoms attached to R^7, R^{11}, R^{15}, R^{18}, or R^{21} can serve as the point of attachment of R^3 to the isoquinoline ring; likewise, any one of the carbon atoms attached to R^8, R^9, R^{10}, R^{12}, R^{13}, R^{14}, R^{16}, R^{17}, R^{19}, R^{20}, R^{22}, R^{23}, R^{24}, R^{25}, R^{26}, R^{27}, R^{28}, R^{29}, R^{30}, R^{31}, R^{32}, R^{33}, R^{34}, or R^{35} can serve as the point of attachment of R^3 to the isoquinoline ring.

In some embodiments, R^6 is selected from the group consisting of —(C_{1-4} alkylene)$_p$heterocyclyl optionally substituted with 1-10 (e.g., 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2,

1) R^{36}, —(C_{1-4} alkylene)$_p$carbocyclyl optionally substituted with 1-12 (e.g., 1-11, 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R^{37}, —(C_{1-4} alkylene)N(R^{46})(R^{47}), and —CF(C_{1-9} alkyl)$_2$; wherein each alkyl of —CF(C_{1-9} alkyl)$_2$ is, independently, optionally substituted with one or more halides; wherein each —(C_{1-4} alkylene) is, independently, optionally substituted with one or more substituents as defined anywhere herein.

In some embodiments, R^6 is selected from the group consisting of —(C_{1-4} alkylene)$_p$heterocyclyl optionally substituted with 1-10 R^{36}, —(C_{1-4} alkylene)$_p$carbocyclyl optionally substituted with 1-12 R^{37}, —(C_{1-4} alkylene)N(R^{46})(R^{47}), —N(R^{48})(R^{49}), —CF(C_{1-9} alkyl)$_2$, —(C_{1-4} alkylene)$_p$O(C_{3-9} alkyl), and —(C_{2-9} alkynyl) optionally substituted with one or more halides; wherein each alkyl of —CF(C_{1-9} alkyl)$_2$ is, independently, optionally substituted with one or more halides; wherein each —(C_{1-4} alkylene) is, independently, optionally substituted with one or more substituents as defined anywhere herein.

In some embodiments, there is the proviso that R^6 is not unsubstituted —(CH_2)tetrahydropyranyl.

In some embodiments, R^7 is selected from the group consisting of a single bond, H, unsubstituted —(C_{1-9} alkyl), unsubstituted —(C_{2-9} alkenyl), unsubstituted —(C_{2-9} alkynyl), unsubstituted —(C_{1-9} haloalkyl), —(C_{1-4} alkylene)$_p$ heterocyclyl optionally substituted with 1-10 (e.g., 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R^{38}, and -carbocyclyl optionally substituted with 1-12 (e.g., 1-11, 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R^{39}; wherein each —(C_{1-4} alkylene) is, independently, optionally substituted with one or more substituents as defined anywhere herein.

In some embodiments, R^7 is selected from the group consisting of a single bond, H, unsubstituted —(C_{1-9} alkyl), unsubstituted —(C_{2-9} alkenyl), unsubstituted —(C_{2-9} alkynyl), unsubstituted —(C_{1-9} haloalkyl), —(C_{1-4} alkylene)OR^{42}, —(C_{1-4} alkylene)$_p$heterocyclyl optionally substituted with 1-10 R^{38}, and -carbocyclyl optionally substituted with 1-12 R^{39}; wherein —(C_{1-4} alkylene) is, optionally substituted with one or more substituents as defined anywhere herein.

In some embodiments, R^8, R^9, and R^{10} are independently selected from the group consisting of a single bond, H, halide, unsubstituted —(C_{1-9} alkyl), unsubstituted —(C_{2-9} alkenyl), unsubstituted —(C_{2-9} alkynyl), unsubstituted —(C_{1-9} haloalkyl), —(C_{1-4} alkylene)$_p$heterocyclyl optionally substituted with 1-10 (e.g., 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R^{38}, and -carbocyclyl optionally substituted with 1-12 (e.g., 1-11, 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R^{39}; wherein each —(C_{1-4} alkylene) is, independently, optionally substituted with one or more substituents as defined anywhere herein.

In some embodiments, R^8, R^9, and R^{10} are independently selected from the group consisting of a single bond, H, halide, unsubstituted —(C_{1-9} alkyl), unsubstituted —(C_{2-9} alkenyl), unsubstituted —(C_{2-9} alkynyl), unsubstituted —(C_{1-9} haloalkyl), —N(R^{53})$_2$, —(C_{1-4} alkylene)$_p$OR^{42}, —(C_{1-4} alkylene)$_p$heterocyclyl optionally substituted with 1-10 R^{38}, and -carbocyclyl optionally substituted with 1-12 R^{39}; wherein each —(C_{1-4} alkylene) is, independently, optionally substituted with one or more substituents as defined anywhere herein.

In some embodiments, one of R^7 and R^8, R^8 and R^9, or R^9 and R^{10} are taken together to form a ring which is selected from the group consisting of -heterocyclyl optionally substituted with 1-10 (e.g., 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R^{40} and -carbocyclyl optionally substituted with 1-12 (e.g., 1-11, 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R^{41}.

In some embodiments, R^{11} is selected from the group consisting of a single bond, H, unsubstituted —(C_{1-9} alkyl), unsubstituted —(C_{2-9} alkenyl), unsubstituted —(C_{2-9} alkynyl), unsubstituted —(C_{1-9} haloalkyl), —(C_{1-4} alkylene)$_p$ heterocyclyl optionally substituted with 1-10 (e.g., 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R^{38}, and -carbocyclyl optionally substituted with 1-12 (e.g., 1-11, 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R^{39}; wherein —(C_{1-4} alkylene) is, optionally substituted with one or more substituents as defined anywhere herein.

In some embodiments, R^{11} is selected from the group consisting of a single bond, H, unsubstituted —(C_{1-9} alkyl), unsubstituted —(C_{2-9} alkenyl), unsubstituted —(C_{2-9} alkynyl), unsubstituted —(C_{1-9} haloalkyl), —(C_{1-4} alkylene)OR^{42}, —(C_{1-4} alkylene)$_p$heterocyclyl optionally substituted with 1-10 R^{38}, and -carbocyclyl optionally substituted with 1-12 R^{39}; wherein —(C_{1-4} alkylene) is, optionally substituted with one or more substituents as defined anywhere herein.

In some embodiments, R^{12}, R^{13}, and R^{14} are independently selected from the group consisting of a single bond, H, halide, unsubstituted —(C_{1-9} alkyl), unsubstituted —(C_{2-9} alkenyl), unsubstituted —(C_{2-9} alkynyl), unsubstituted —(C_{1-9} haloalkyl), —(C_{1-4} alkylene)$_p$heterocyclyl optionally substituted with 1-10 (e.g., 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R^{38}, and -carbocyclyl optionally substituted with 1-12 (e.g., 1-11, 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R^{39}; wherein each —(C_{1-4} alkylene) is, independently, optionally substituted with one or more substituents as defined anywhere herein.

In some embodiments, R^{12}, R^{13}, and R^{14} are independently selected from the group consisting of a single bond, H, halide, unsubstituted —(C_{1-9} alkyl), unsubstituted —(C_{2-9} alkenyl), unsubstituted —(C_{2-9} alkynyl), unsubstituted —(C_{1-9} haloalkyl), —N(R^{53})$_2$, —(C_{1-4} alkylene)$_p$ OR^{42}, —(C_{1-4} alkylene)$_p$heterocyclyl optionally substituted with 1-10 R^{38}, and -carbocyclyl optionally substituted with 1-12 R^{39}; wherein each —(C_{1-4} alkylene) is, independently, optionally substituted with one or more substituents as defined anywhere herein.

In some embodiments, one of R^{11} and R^{12}, R^{12} and R^{13}, or R^{14} and R^{11} are taken together to form a ring which is selected from the group consisting of -heterocyclyl optionally substituted with 1-10 (e.g., 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R^{40} and -carbocyclyl optionally substituted with 1-12 (e.g., 1-11, 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R^{41}.

In some embodiments, R^{15} is selected from the group consisting of H, unsubstituted —(C_{1-9} alkyl), unsubstituted —(C_{2-9} alkenyl), unsubstituted —(C_{2-9} alkynyl), unsubstituted —(C_{1-9} haloalkyl), —(C_{1-4} alkylene)$_p$heterocyclyl optionally substituted with 1-10 (e.g., 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R^{38}, and -carbocyclyl optionally substituted with 1-12 (e.g., 1-11, 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R^{39}; wherein —(C_{1-4} alkylene) is, optionally substituted with one or more substituents as defined anywhere herein.

In some embodiments, R^{15} is selected from the group consisting of a single bond, H, unsubstituted —(C_{1-9} alkyl), unsubstituted —(C_{2-9} alkenyl), unsubstituted —(C_{2-9} alkynyl), unsubstituted —(C_{1-9} haloalkyl), —(C_{1-4} alkylene)OR^{42}, —(C_{1-4} alkylene)$_p$heterocyclyl optionally substituted with 1-10 R^{38}, and -carbocyclyl optionally substituted with 1-12 R^{39}; wherein —(C_{1-4} alkylene) is, optionally substituted with one or more substituents as defined anywhere herein.

In some embodiments, R^{16} and R^{17} are independently selected from the group consisting of H, halide, unsubstituted —(C_{1-9} alkyl), unsubstituted —(C_{2-9} alkenyl), unsubstituted —(C_{2-9} alkynyl), unsubstituted —(C_{1-9} haloalkyl), —(C_{1-4} alkylene)$_p$heterocyclyl optionally substituted with 1-10 (e.g., 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R^{38}, and -carbocyclyl optionally substituted with 1-12 (e.g., 1-11, 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R^{39}; wherein each —(C_{1-4} alkylene) is, independently, optionally substituted with one or more substituents as defined anywhere herein.

In some embodiments, R^{16} and R^{17} are independently selected from the group consisting of a single bond, H, halide, unsubstituted —(C_{1-9} alkyl), unsubstituted —(C_{2-9} alkenyl), unsubstituted —(C_{2-9} alkynyl), unsubstituted —(C_{1-9} haloalkyl), —$N(R^{53})_2$, —(C_{1-4} alkylene)$_p$$OR^{42}$, —($C_{1-4}$ alkylene)$_p$heterocyclyl optionally substituted with 1-10 R^{38}, and -carbocyclyl optionally substituted with 1-12 R^{39}; wherein each —(C_{1-4} alkylene) is, independently, optionally substituted with one or more substituents as defined anywhere herein.

In some embodiments, one of R^{15} and R^{16} or R^{16} and R^{17} are taken together to form a ring which is selected from the group consisting of -heterocyclyl optionally substituted with 1-10 (e.g., 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R^{40} and -carbocyclyl optionally substituted with 1-12 (e.g., 1-11, 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R^{41}.

In some embodiments, R^{18} is selected from the group consisting of a single bond, H, unsubstituted —(C_{1-9} alkyl), unsubstituted —(C_{2-9} alkenyl), unsubstituted —(C_{2-9} alkynyl), unsubstituted —(C_{1-9} haloalkyl), —(C_{1-4}alkylene)$_p$heterocyclyl optionally substituted with 1-10 (e.g., 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R^{38}, and -carbocyclyl optionally substituted with 1-12 (e.g., 1-11, 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R^{39}; wherein —(C_{1-4} alkylene) is, optionally substituted with one or more substituents as defined anywhere herein.

In some embodiments, R^{18} is selected from the group consisting of a single bond, H, unsubstituted —(C_{1-9} alkyl), unsubstituted —(C_{2-9} alkenyl), unsubstituted —(C_{2-9} alkynyl), unsubstituted —(C_{1-9} haloalkyl), —(C_{1-4} alkylene)$_p$$OR^{42}$, —($C_{1-4}$ alkylene)$_p$heterocyclyl optionally substituted with 1-10 R^{38}, and -carbocyclyl optionally substituted with 1-12 R^{39}; wherein —(C_{1-4} alkylene) is, optionally substituted with one or more substituents as defined anywhere herein.

In some embodiments, R^{19} and R^{20} are independently selected from the group consisting of a single bond, H, halide, unsubstituted —(C_{1-9} alkyl), unsubstituted —(C_{2-9} alkenyl), unsubstituted —(C_{2-9} alkynyl), unsubstituted —(C_{1-9} haloalkyl), —(C_{1-4} alkylene)$_p$heterocyclyl optionally substituted with 1-10 (e.g., 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R^{38}, and -carbocyclyl optionally substituted with 1-12 (e.g., 1-11, 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R^{39}; wherein each —(C_{1-4} alkylene) is, independently, optionally substituted with one or more substituents as defined anywhere herein.

In some embodiments, R^{19} and R^{20} are independently selected from the group consisting of a single bond, H, halide, unsubstituted —(C_{1-9} alkyl), unsubstituted —(C_{2-9} alkenyl), unsubstituted —(C_{2-9} alkynyl), unsubstituted —(C_{1-9} haloalkyl), —$N(R^{53})_2$, —(C_{1-4} alkylene)$_p$$OR^{42}$, —($C_{1-4}$ alkylene)$_p$heterocyclyl optionally substituted with 1-10 R^{38}, and -carbocyclyl optionally substituted with 1-12 R^{39}; wherein each —(C_{1-4} alkylene) is, independently, optionally substituted with one or more substituents as defined anywhere herein

In some embodiments, one of R^{18} and R^{19} or R^{18} and R^{20} are taken together to form a heterocyclyl optionally substituted with 1-10 (e.g., 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R^{40}.

In some embodiments, R^{21} is selected from the group consisting of a single bond, H, unsubstituted —(C_{1-9} alkyl), unsubstituted —(C_{2-9} alkenyl), unsubstituted —(C_{2-9} alkynyl), unsubstituted —(C_{1-9} haloalkyl), —(C_{1-4}alkylene)$_p$heterocyclyl optionally substituted with 1-10 (e.g., 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R^{38}, and -carbocyclyl optionally substituted with 1-12 (e.g., 1-11, 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R^{39}; wherein —(C_{1-4} alkylene) is, optionally substituted with one or more substituents as defined anywhere herein.

In some embodiments, R^{21} is selected from the group consisting of a single bond, H, unsubstituted —(C_{1-9} alkyl), unsubstituted —(C_{2-9} alkenyl), unsubstituted —(C_{2-9} alkynyl), unsubstituted —(C_{1-9} haloalkyl), —(C_{1-4} alkylene)$_p$$OR^{42}$, —($C_{1-4}$ alkylene)$_p$heterocyclyl optionally substituted with 1-10 R^{38}, and -carbocyclyl optionally substituted with 1-12 R^{39}; wherein —(C_{1-4} alkylene) is, optionally substituted with one or more substituents as defined anywhere herein.

In some embodiments, R^{22} and R^{23} are independently selected from the group consisting of a single bond, H, halide, unsubstituted —(C_{1-9} alkyl), unsubstituted —(C_{2-9} alkenyl), unsubstituted —(C_{2-9} alkynyl), unsubstituted —(C_{1-9} haloalkyl), —(C_{1-4} alkylene)$_p$heterocyclyl optionally substituted with 1-10 (e.g., 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R^{38}, and -carbocyclyl optionally substituted with 1-12 (e.g., 1-11, 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R^{39}; wherein each —(C_{1-4} alkylene) is, independently, optionally substituted with one or more substituents as defined anywhere herein.

In some embodiments, R^{22} and R^{23} are independently selected from the group consisting of a single bond, H, halide, unsubstituted —(C_{1-9} alkyl), unsubstituted —(C_{2-9} alkenyl), unsubstituted —(C_{2-9} alkynyl), unsubstituted —(C_{1-9} haloalkyl), —$N(R^{53})_2$, —(C_{1-4} alkylene)$_p$$OR^{42}$, —($C_{1-4}$ alkylene)$_p$heterocyclyl optionally substituted with 1-10 R^{38}, and -carbocyclyl optionally substituted with 1-12 R^{39}; wherein each —(C_{1-4} alkylene) is, independently, optionally substituted with one or more substituents as defined anywhere herein.

In some embodiments, R^{22} and R^{23} are taken together to form a ring which is selected from the group consisting of -heterocyclyl optionally substituted with 1-10 (e.g., 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R^{40} and -carbocyclyl optionally substituted with 1-12 (e.g., 1-11, 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R^{41}.

In some embodiments, R^{24}, R^{25}, and R^{26} are independently selected from the group consisting of a single bond, H, halide, unsubstituted —(C_{1-9} alkyl), unsubstituted —(C_{2-9} alkenyl), unsubstituted —(C_{2-9} alkynyl), unsubstituted —(C_{1-9} haloalkyl), —(C_{1-4} alkylene)$_p$heterocyclyl optionally substituted with 1-10 (e.g., 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R^{38}, and -carbocyclyl optionally substituted with 1-12 (e.g., 1-11, 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R^{39}; wherein each —(C_{1-4} alkylene) is, independently, optionally substituted with one or more substituents as defined anywhere herein.

In some embodiments, R^{24}, R^{25}, and R^{26} are independently selected from the group consisting of a single bond, H, halide, unsubstituted —(C_{1-9} alkyl), unsubstituted —(C_{2-9} alkenyl), unsubstituted —(C_{2-9} alkynyl), unsubstituted —(C_{1-9} haloalkyl), —$N(R^{53})_2$, —(C_{1-4} alkylene)$_p$ OR^{42}, —(C_{1-4} alkylene)$_p$heterocyclyl optionally substi-

tuted with 1-10 R^{38}, and -carbocyclyl optionally substituted with 1-12 R^{39}; wherein each —(C_{1-4} alkylene) is, independently, optionally substituted with one or more substituents as defined anywhere herein.

In some embodiments, there is the proviso that when R^{25} is a single bond connecting R^3 to the isoquinoline ring, R^{24} and R^{26} are not methyls.

In some embodiments, there is the proviso that when R^{25} is a single bond connecting R^3 to the isoquinoline ring, R^{24} and R^{26} are not both methyls.

In some embodiments, there is the proviso that when R^{25} is a single bond connecting R^3 to the isoquinoline ring, R^{24} and R^{26} are not selected from the group consisting of a single bond, H, halide, unsubstituted —(C_{1-2} alkyl), unsubstituted —(C_2 alkenyl), unsubstituted —(C_2 alkynyl), unsubstituted —(C_{1-2} haloalkyl).

In some embodiments, one of R^{24} and R^{25} or R^{25} and R^{26} are taken together to form a ring which is selected from the group consisting of -heterocyclyl optionally substituted with 1-10 (e.g., 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R^{40} and -carbocyclyl optionally substituted with 1-12 (e.g., 1-11, 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R^{41}.

In some embodiments, R^{27}, R^{28}, and R^{29} are independently selected from the group consisting of a single bond, H, halide, unsubstituted —(C_{1-9} alkyl), unsubstituted —(C_{2-9} alkenyl), unsubstituted —(C_{2-9} alkynyl), unsubstituted —(C_{1-9} haloalkyl), —(C_{1-4} alkylene)$_p$heterocyclyl optionally substituted with 1-10 (e.g., 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R^{38}, and -carbocyclyl optionally substituted with 1-12 (e.g., 1-11, 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R^{39}; wherein each —(C_{1-4} alkylene) is, independently, optionally substituted with one or more substituents as defined anywhere herein.

In some embodiments, R^{27}, R^{28}, and R^{29} are independently selected from the group consisting of a single bond, H, halide, unsubstituted —(C_{1-9} alkyl), unsubstituted —(C_{2-9} alkenyl), unsubstituted —(C_{2-9} alkynyl), unsubstituted —(C_{1-9} haloalkyl), —$N(R^{53})_2$, —(C_{1-4} alkylene)$_p$ OR^{42}, —(C_{1-4} alkylene)$_p$heterocyclyl optionally substituted with 1-10 R^{38}, and -carbocyclyl optionally substituted with 1-12 R^{39}; wherein each —(C_{1-4} alkylene) is, independently, optionally substituted with one or more substituents as defined anywhere herein.

In some embodiments, R^{27} and R^{28} are taken together to form a ring which is selected from the group consisting of -heterocyclyl optionally substituted with 1-10 (e.g., 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R^{40} and -carbocyclyl optionally substituted with 1-12 (e.g., 1-11, 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R^{41}.

In some embodiments, R^{30} and R^{31} are independently selected from the group consisting of a single bond, H, halide, unsubstituted —(C_{1-9} alkyl), unsubstituted —(C_{2-9} alkenyl), unsubstituted —(C_{2-9} alkynyl), unsubstituted —(C_{1-9} haloalkyl), —(C_{1-4} alkylene)$_p$heterocyclyl optionally substituted with 1-10 (e.g., 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R^{38}, and -carbocyclyl optionally substituted with 1-12 (e.g., 1-11, 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R^{39}; wherein each —(C_{1-4} alkylene) is, independently, optionally substituted with one or more substituents as defined anywhere herein.

In some embodiments, R^{30} and R^{31} are independently selected from the group consisting of a single bond, H, halide, unsubstituted —(C_{1-9} alkyl), unsubstituted —(C_{2-9} alkenyl), unsubstituted —(C_{2-9} alkynyl), unsubstituted —(C_{1-9} haloalkyl), —$N(R^{53})_2$, —(C_{1-4} alkylene)$_p$$OR^{42}$, —($C_{1-4}$ alkylene)$_p$heterocyclyl optionally substituted with 1-10 R^{38}, and -carbocyclyl optionally substituted with 1-12 R^{39}; wherein each —(C_{1-4} alkylene) is, independently, optionally substituted with one or more substituents as defined anywhere herein.

In some embodiments, R^{30} and R^{31} are taken together to form a ring which is selected from the group consisting of -heterocyclyl optionally substituted with 1-10 (e.g., 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R^{40} and -carbocyclyl optionally substituted with 1-12 (e.g., 1-11, 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R^{41}.

In some embodiments, R^{32} and R^{33} are independently selected from the group consisting of a single bond, H, halide, unsubstituted —(C_{1-9} alkyl), unsubstituted —(C_{2-9} alkenyl), unsubstituted —(C_{2-9} alkynyl), unsubstituted —(C_{1-9} haloalkyl), —(C_{1-4} alkylene)$_p$heterocyclyl optionally substituted with 1-10 (e.g., 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R^{38}, and -carbocyclyl optionally substituted with 1-12 (e.g., 1-11, 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R^{39}; wherein each —(C_{1-4} alkylene) is, independently, optionally substituted with one or more substituents as defined anywhere herein.

In some embodiments, R^{32} and R^{33} are independently selected from the group consisting of a single bond, H, halide, unsubstituted —(C_{1-9} alkyl), unsubstituted —(C_{2-9} alkenyl), unsubstituted —(C_{2-9} alkynyl), unsubstituted —(C_{1-9} haloalkyl), —$N(R^{53})_2$, —(C_{1-4} alkylene)$_p$$OR^{42}$, —($C_{1-4}$ alkylene)$_p$heterocyclyl optionally substituted with 1-10 R^{38}, and -carbocyclyl optionally substituted with 1-12 R^{39}; wherein each —(C_{1-4} alkylene) is, independently, optionally substituted with one or more substituents as defined anywhere herein.

In some embodiments, R^{34} and R^{35} are independently selected from the group consisting of a single bond, H, halide, unsubstituted —(C_{1-9} alkyl), unsubstituted —(C_{2-9} alkenyl), unsubstituted —(C_{2-9} alkynyl), unsubstituted —(C_{1-9} haloalkyl), —(C_{1-4} alkylene)$_p$heterocyclyl optionally substituted with 1-10 (e.g., 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R^{38}, and -carbocyclyl optionally substituted with 1-12 (e.g., 1-11, 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R^{39}; wherein each —(C_{1-4} alkylene) is, independently, optionally substituted with one or more substituents as defined anywhere herein.

In some embodiments, R^{34} and R^{35} are independently selected from the group consisting of a single bond, H, halide, unsubstituted —(C_{1-9} alkyl), unsubstituted —(C_{2-9} alkenyl), unsubstituted —(C_{2-9} alkynyl), unsubstituted —(C_{1-9} haloalkyl), —$N(R^{53})_2$, —(C_{1-4} alkylene)$_p$$OR^{42}$, —($C_{1-4}$ alkylene)$_p$heterocyclyl optionally substituted with 1-10 R^{38}, and -carbocyclyl optionally substituted with 1-12 R^{39}; wherein each —(C_{1-4} alkylene) is, independently, optionally substituted with one or more substituents as defined anywhere herein.

In some embodiments, R^{34} and R^{35} are taken together to form a ring which is selected from the group consisting of -heterocyclyl optionally substituted with 1-10 (e.g., 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R^{40} and -carbocyclyl optionally substituted with 1-12 (e.g., 1-11, 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R^{41}.

In some embodiments, each R^{36} is independently selected from the group consisting of halide, unsubstituted —(C_{1-9} alkyl), unsubstituted —(C_{2-9} alkenyl), unsubstituted —(C_{2-9} alkynyl), unsubstituted —(C_{1-9} haloalkyl), —(C_{1-4} alkylene)$_p$$OR^{42}$, —($C_{1-4}$ alkylene)$_p$heterocyclyl optionally substituted with 1-10 (e.g., 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R^{43}, and —(C_{1-4} alkylene)$_p$carbocyclyl optionally substituted with 1-12 (e.g., 1-11, 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R^{44}; wherein each —(C_{1-4} alkylene) is,

independently, optionally substituted with one or more substituents as defined anywhere herein.

In some embodiments, each R^{36} is independently selected from the group consisting of halide, unsubstituted —(C_{1-9} alkyl), unsubstituted —(C_{2-9} alkenyl), unsubstituted —(C_{2-9} alkynyl), unsubstituted —(C_{1-9} haloalkyl), —(C_{1-4} alkylene)$_p$OR^{42}, —(C_{1-4} alkylene)$_p$heterocyclyl optionally substituted with 1-10 R^{43}, —(C_{1-4} alkylene)$_p$carbocyclyl optionally substituted with 1-12 R^{44}, —C(═O)(R^{50}), —(C_{1-4} alkylene)C(═O)OR^{51}, —(C_{1-4} alkylene)aryl optionally substituted with one or more halides, —(C_{1-4} alkylene)$_p$heteroaryl optionally substituted with one or more halides (e.g. F, Cl, Br, I), and —SO_2(R^{52}); wherein each —(C_{1-4} alkylene) is, independently, optionally substituted with one or more substituents as defined anywhere herein.

In some embodiments, two R^{36} that are attached to the same carbon atom can together represent ═O to form a carbonyl group.

In some embodiments, each R^{37} is independently selected from the group consisting of halide, unsubstituted —(C_{1-9} alkyl), unsubstituted —(C_{2-9} alkenyl), unsubstituted —(C_{2-9} alkynyl), unsubstituted —(C_{1-9} haloalkyl), —(C_{1-4} alkylene)$_p$OR^{42}, —(C_{1-4} alkylene)$_p$heterocyclyl optionally substituted with 1-10 (e.g., 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R^{43}, and —(C_{1-4} alkylene)$_p$carbocyclyl optionally substituted with 1-12 (e.g., 1-11, 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R^{44}; wherein each —(C_{1-4} alkylene) is, independently, optionally substituted with one or more substituents as defined anywhere herein.

In some embodiments, each R^{37} is independently selected from the group consisting of halide, unsubstituted —(C_{1-9} alkyl), unsubstituted —(C_{2-9} alkenyl), unsubstituted —(C_{2-9} alkynyl), unsubstituted —(C_{1-9} haloalkyl), —(C_{1-4} alkylene)$_p$OR^{42}, —N(R^{53})$_2$, —C(═O)(R^{50}), —C(═O)OR^{51}, —(C_{1-4} alkylene)$_p$heterocyclyl optionally substituted with 1-10 R^{43}, and —(C_{1-4} alkylene)$_p$carbocyclyl optionally substituted with 1-12 R^{44}; wherein each —(C_{1-4} alkylene) is, independently, optionally substituted with one or more substituents as defined anywhere herein.

In some embodiments, each R^{38} is independently selected from the group consisting of halide, unsubstituted —(C_{1-5} alkyl), unsubstituted —(C_{2-5} alkenyl), unsubstituted —(C_{2-5} alkynyl), unsubstituted —(C_{1-5} haloalkyl), —CN, and —(C_{1-4} alkylene)$_p$carbocyclyl optionally substituted with 1-12 (e.g., 1-11, 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R^{44}; wherein each —(C_{1-4} alkylene) is, independently, optionally substituted with one or more substituents as defined anywhere herein.

In some embodiments, each R^{39} is independently selected from the group consisting of halide, unsubstituted —(C_{1-5} alkyl), unsubstituted —(C_{2-5} alkenyl), unsubstituted —(C_{2-5} alkynyl), unsubstituted —(C_{1-5} haloalkyl), —CN, and —(C_{1-4} alkylene)$_p$carbocyclyl optionally substituted with 1-12 (e.g., 1-11, 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R^{44}; wherein each —(C_{1-4} alkylene) is, independently, optionally substituted with one or more substituents as defined anywhere herein.

In some embodiments, each R^{40} is independently selected from the group consisting of halide, unsubstituted —(C_{1-5} alkyl), unsubstituted —(C_{2-5} alkenyl), unsubstituted —(C_{2-5} alkynyl), unsubstituted —(C_{1-5} haloalkyl), —CN, and —(C_{1-4} alkylene)$_p$carbocyclyl optionally substituted with 1-12 (e.g., 1-11, 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R^{44}; wherein each —(C_{1-4} alkylene) is, independently, optionally substituted with one or more substituents as defined anywhere herein.

In some embodiments, each R^{41} is independently selected from the group consisting of halide, unsubstituted —(C_{1-5} alkyl), unsubstituted —(C_{2-5} alkenyl), unsubstituted —(C_{2-5} alkynyl), unsubstituted —(C_{1-5} haloalkyl), and —CN.

In some embodiments, each R^{42} is independently selected from the group consisting of unsubstituted —(C_{1-5} alkyl), unsubstituted —(C_{2-5} alkenyl), unsubstituted —(C_{2-5} alkynyl), unsubstituted —(C_{1-5} haloalkyl), and —(C_{1-4} alkylene)$_p$carbocyclyl optionally substituted with 1-12 (e.g., 1-11, 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R^{44}; wherein each —(C_{1-4} alkylene) is, independently, optionally substituted with one or more substituents as defined anywhere herein.

In some embodiments, each R^{43} is independently selected from the group consisting of halide, unsubstituted —(C_{1-5} alkyl), unsubstituted —(C_{2-5} alkenyl), unsubstituted —(C_{2-5} alkynyl), unsubstituted —(C_{1-5} haloalkyl), —CN, and —(C_{1-4} alkylene)$_p$carbocyclyl optionally substituted with 1-12 (e.g., 1-11, 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R^{44}; wherein each —(C_{1-4} alkylene) is, independently, optionally substituted with one or more substituents as defined anywhere herein.

In some embodiments, each R^{44} is independently selected from the group consisting of halide, unsubstituted —(C_{1-5} alkyl), unsubstituted —(C_{2-5} alkenyl), unsubstituted —(C_{2-5} alkynyl), unsubstituted —(C_{1-5} haloalkyl), and —CN.

In some embodiments, each R^{45} is independently selected from the group consisting of H, unsubstituted —(C_{1-9} alkyl), unsubstituted —(C_{2-9} alkenyl), unsubstituted —(C_{2-9} alkynyl), unsubstituted —(C_{1-9} haloalkyl), —(C_{1-4} alkylene)$_p$ heterocyclyl optionally substituted with 1-10 (e.g., 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R^{38}, and -carbocyclyl optionally substituted with 1-12 (e.g., 1-11, 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R^{39}; wherein each —(C_{1-4} alkylene) is, independently, optionally substituted with one or more substituents as defined anywhere herein.

In some embodiments, each R^{45} is independently selected from the group consisting of H, unsubstituted —(C_{1-9} alkyl), unsubstituted —(C_{2-9} alkenyl), unsubstituted —(C_{2-9} alkynyl), unsubstituted —(C_{1-9} haloalkyl), —N(R^{53})$_2$, —(C_{1-4} alkylene)$_p$OR^{42}, —(C_{1-4} alkylene)$_p$heterocyclyl optionally substituted with 1-10 R^{38}, and -carbocyclyl optionally substituted with 1-12 R^{39}; wherein each —(C_{1-4} alkylene) is, independently, optionally substituted with one or more substituents as defined anywhere herein.

In some embodiments, two adjacent R^{45} groups are taken together to form a ring which is selected from the group consisting of -heterocyclyl optionally substituted with 1-10 (e.g., 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R^{40} and -carbocyclyl optionally substituted with 1-12 (e.g., 1-11, 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R^{41}.

In some embodiments, R^{46} is attached to the nitrogen and is selected from the group consisting of H, unsubstituted —(C_{1-9} alkyl), unsubstituted —(C_{2-9} alkenyl), unsubstituted —(C_{2-9} alkynyl), unsubstituted —(C_{1-9} haloalkyl), —(C_{1-4} alkylene)$_p$heterocyclyl optionally substituted with 1-10 (e.g., 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R^{38}, and -carbocyclyl optionally substituted with 1-12 (e.g., 1-11, 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R^{39}; wherein —(C_{1-4} alkylene) is, optionally substituted with one or more substituents as defined anywhere herein.

In some embodiments, R^{47} is attached to the nitrogen and is selected from the group consisting of unsubstituted —(C_{1-9} alkyl), unsubstituted —(C_{2-9} alkenyl), unsubstituted —(C_{2-9} alkynyl), unsubstituted —(C_{1-9} haloalkyl), —(C_{1-4} alkylene)$_p$heterocyclyl optionally substituted with 1-10 (e.g., 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R^{38}, and

-carbocyclyl optionally substituted with 1-12 (e.g., 1-11, 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R^{39}; wherein —(C_{1-4} alkylene) is, optionally substituted with one or more substituents as defined anywhere herein.

In some embodiments, R^{48} is attached to the nitrogen and selected from the group consisting of H, unsubstituted —(C_{1-5} alkyl), unsubstituted —(C_{2-5}alkenyl), unsubstituted —(C_{2-5} alkynyl), and unsubstituted —(C_{1-5} haloalkyl).

In some embodiments, R^{49} is attached to the nitrogen and is selected from the group consisting of —(C_{1-4} alkylene)$_p$heterocyclyl optionally substituted with 1-10 R^{38}, and —(C_{1-4} alkylene)$_p$carbocyclyl optionally substituted with 1-12 R^{39}; wherein each —(C_{1-4} alkylene) is, independently, optionally substituted with one or more substituents as defined anywhere herein.

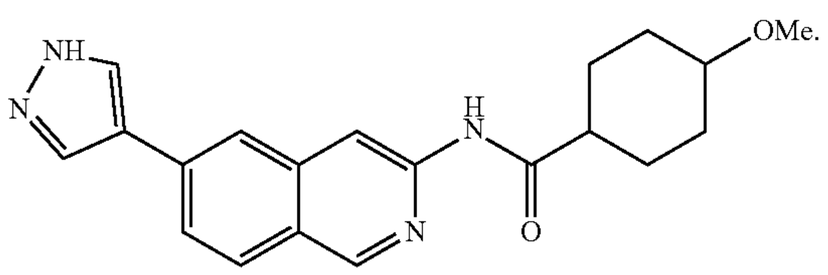
In some embodiments, R^{50} is selected from the group consisting of H, unsubstituted —(C_{3-5} alkyl), unsubstituted —(C_{2-5} alkenyl), unsubstituted —(C_{2-5} alkynyl), unsubstituted —(C_{1-5} haloalkyl), —(C_{1-4}alkylene)$_p$aryl optionally substituted with one or more halides or unsubstituted —(C_{1-5} alkyl), —(C_{1-4} alkylene)$_p$heteroaryl optionally substituted with one or more halides or unsubstituted —(C_{1-5} alkyl), and —(C_{1-4} alkylene)$_p$heterocyclyl optionally substituted with one or more halides or one or more unsubstituted —(C_{1-5} alkyl); wherein each —(C_{1-4} alkylene) is, independently, optionally substituted with one or more substituents as defined anywhere herein.

In some embodiments, R^{51} is selected from the group consisting of H, unsubstituted —(C_{1-5} alkyl), unsubstituted —(C_{2-5} alkenyl), unsubstituted —(C_{2-5} alkynyl), unsubstituted —(C_{1-5} haloalkyl), —(C_{1-4} alkylene)$_p$aryl optionally substituted with one or more halides or unsubstituted —(C_{1-5} alkyl), —(C_{1-4} alkylene)$_p$heteroaryl optionally substituted with one or more halides or unsubstituted —(C_{1-5} alkyl), and —(C_{1-4} alkylene)$_p$heterocyclyl optionally substituted with one or more halides or one or more unsubstituted —(C_{1-5} alkyl); wherein each —(C_{1-4} alkylene) is, independently, optionally substituted with one or more substituents as defined anywhere herein.

In some embodiments, R^{52} is selected from the group consisting of unsubstituted —(C_{1-5} alkyl), unsubstituted —(C_{2-5} alkenyl), unsubstituted —(C_{2-5} alkynyl), unsubstituted —(C_{1-5} haloalkyl), —(C_{1-4} alkylene)$_p$aryl optionally substituted with one or more halides or unsubstituted —(C_{1-5} alkyl), —(C_{1-4} alkylene)$_p$heteroaryl optionally substituted with one or more halides or unsubstituted —(C_{1-5} alkyl), and —(C_{1-4} alkylene)$_p$heterocyclyl optionally substituted with one or more halides or one or more unsubstituted —(C_{1-5} alkyl); wherein —(C_{1-4} alkylene) is, optionally substituted with one or more substituents as defined anywhere herein.

In some embodiments, each R^{53} is independently selected from the group consisting of H, unsubstituted —(C_{1-5} alkyl), unsubstituted —(C_{2-5} alkenyl), and unsubstituted —(C_{2-5} alkynyl).

In some embodiments, there is the proviso that Formula I is not a structure selected from the group consisting of:



In some embodiments, the carbocyclyl of —(C_{1-4} alkylene)$_p$carbocyclyl is optionally substituted with 1-12 R^{37}.

In some embodiments, the —(C_{1-4} alkylene) of —(C_{1-4} alkylene)$_p$carbocyclyl is optionally substituted with 1-12 R^{37}.

In some embodiments, the heterocyclyl of —(C_{1-4} alkylene)$_p$heterocyclyl is optionally substituted with 1-10 R^{38}.

In some embodiments, the —(C_{1-4} alkylene) of —(C_{1-4} alkylene)$_p$heterocyclyl is optionally substituted with 1-10 R^{38}.

In some embodiments, the carbocyclyl of —(C_{1-4} alkylene)$_p$carbocyclyl is optionally substituted with 1-12 R^{44}.

In some embodiments, the —(C_{1-4} alkylene) of —(C_{1-4} alkylene)$_p$carbocyclyl is optionally substituted with 1-12 R^{44}.

In some embodiments, the heterocyclyl of —(C_{1-4} alkylene)$_p$heterocyclyl is optionally substituted with 1-10 R^{43}.

In some embodiments, the —(C_{1-4} alkylene) of —(C_{1-4} alkylene)$_p$heterocyclyl is optionally substituted with 1-10 R^{43}.

In some embodiments, —(C_{1-4} alkylene) is optionally substituted with 1-5 halide or 1-5 unsubstituted —(C_{1-3} alkyl).

In some embodiments, —(C_{1-4} alkylene) is substituted with 1-2 fluorines.

In some embodiments, —(C_{1-4} alkylene) is substituted with 1-2 methyls.

In some embodiments, each X is O or S.

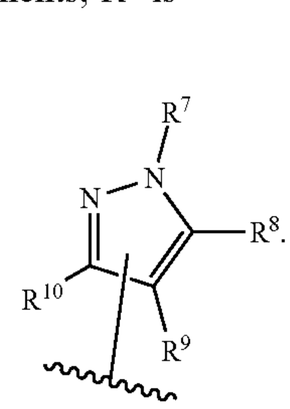
In some embodiments, each m is independently 1 to 4 (e.g., 1-3, 1-2, 1).

In some embodiments, each n is independently 0 to 3 (e.g., 0-2, 0-1, 0).

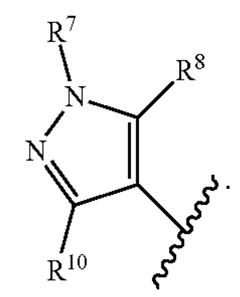
In some embodiments, each p is independently 0 or 1.

In some embodiments, each q is independently 0 to 12 (e.g., 0-11, 0-10, 0-9, 0-8, 0-7, 0-6, 0-5, 0-4, 0-3, 0-2, 0-1, 0).

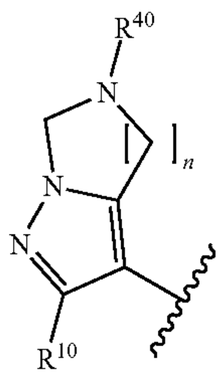
In some embodiments, R^3 is



In certain embodiments, R^9 is a single bond connecting R^3 to the isoquinoline ring, i.e., R^3 has the following formula:



In some embodiments, R^3 is



and n is 1 to 3.

In some embodiments, R^7 is selected from the group consisting of H, unsubstituted —(C_{1-3} alkyl), unsubstituted —(C_{1-2} haloalkyl), and —(C_{3-4} carbocyclyl) optionally substituted with 1-2 R^{39}.

In some embodiments, R^7 is selected from the group consisting of H, methyl, —CF_3, and cyclopropyl optionally substituted with 1-2 R^{39}.

In some embodiments, R^7 is selected from the group consisting of H and methyl.

In some embodiments, R^7 is methyl.

In some embodiments, R^7 is —CD_3.

In some embodiments, R^8 is selected from the group consisting of H, halide, unsubstituted —(C_{1-2} alkyl), unsubstituted —(C_{1-2} haloalkyl), and —(C_{1-2}alkylene)OR^{42}.

In some embodiments, R^8 is selected from the group consisting of H, F, methyl, —CF_3, —(CH_2)OH, and —(CH_2)OMe.

In some embodiments, R^8 is selected from the group consisting of H, F, and methyl.

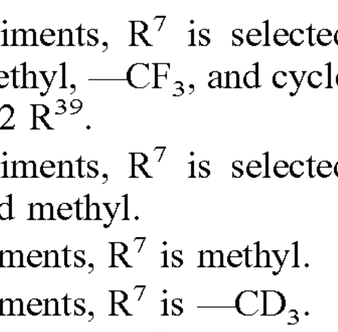
In some embodiments, R^8 is H.

In some embodiments, R^{10} is selected from the group consisting of H and halide.

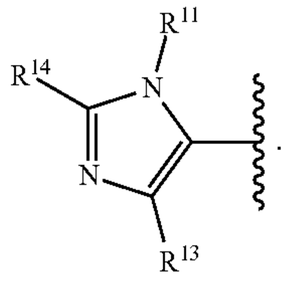
In some embodiments, R^{10} is selected from the group consisting of H and F.

In some embodiments, R^{10} is H.

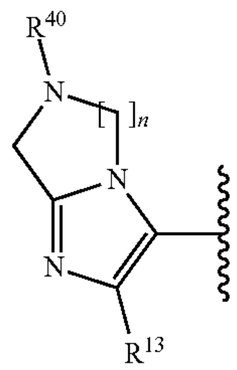
In some embodiments, R^3 is



In certain embodiments, R^{12} is a single bond connecting R^3 to the isoquinoline ring, i.e., R^3 has the following formula:



In some embodiments, R^3 is



and n is 1 to 3.

In some embodiments, R^{11} is selected from the group consisting of H, unsubstituted —(C_{1-3} alkyl), unsubstituted —(C_{1-2} haloalkyl), and —(C_{3-4} carbocyclyl) optionally substituted with 1-2 R^{39}.

In some embodiments, R^{11} is selected from the group consisting of H, methyl, —CF_3, and cyclopropyl optionally substituted with 1-2 R^{39}.

In some embodiments, R^{11} is selected from the group consisting of H and methyl.

In some embodiments, R^{11} is methyl.

In some embodiments, R^{11} is —CD_3.

In some embodiments, R^{13} is selected from the group consisting of H and halide.

In some embodiments, R^{13} is selected from the group consisting of H and F.

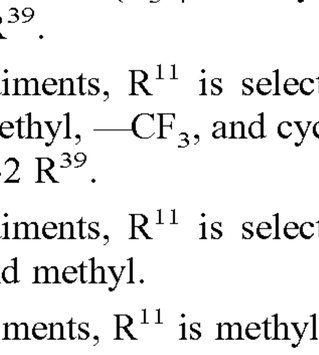
In some embodiments, R^{14} is selected from the group consisting of H, halide, unsubstituted —(C_{1-2} alkyl), and unsubstituted —(C_{1-2}haloalkyl).

In some embodiments, R^{14} is selected from the group consisting of H, F, methyl, and —CF_3.

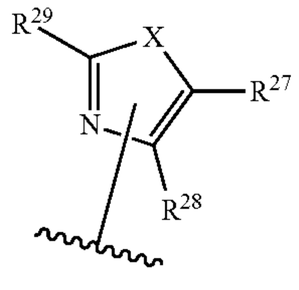
In some embodiments, R^{14} is selected from the group consisting of H and methyl.

In some embodiments, R^{11} and R^{14} are both methyl.

In some embodiments, R^3 is

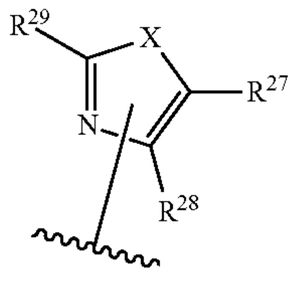


In some embodiments, R^3 is



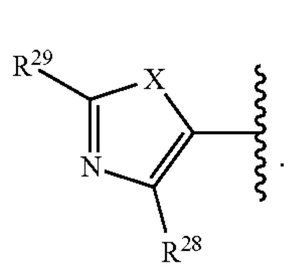
and X is S.

In some embodiments, R^3 is

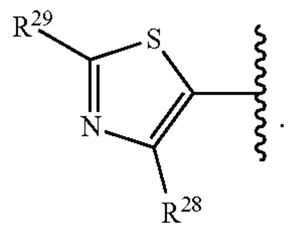


and X is O.

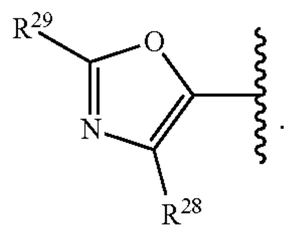
In certain embodiments, R^{27} is a single bond connecting R^3 to the isoquinoline ring, i.e., R^3 has the following formula:



In some embodiments, R^3 is



In some embodiments, R^3 is



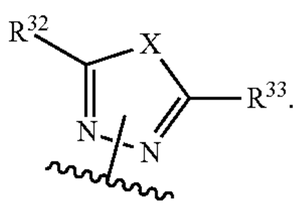
In some embodiments, R^{28} is selected from the group consisting of H and halide.

In some embodiments, R^{28} is selected from the group consisting of H and F.

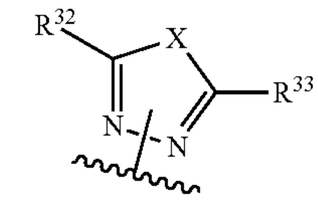
In some embodiments, R^{29} is selected from the group consisting of H, halide, unsubstituted —(C_{1-2} alkyl), and unsubstituted —(C_{1-2}haloalkyl).

In some embodiments, R^{29} is selected from the group consisting of H, F, methyl, and —CF_3.

In some embodiments, R^3 is

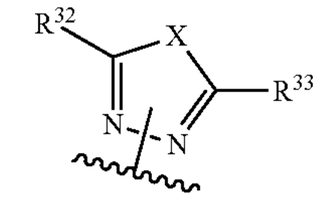


In some embodiments, R^3 is



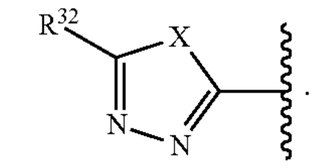
and X is S.

In some embodiments, R^3 is

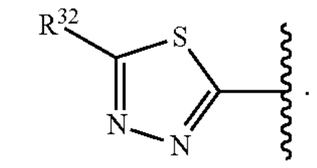


and X is O.

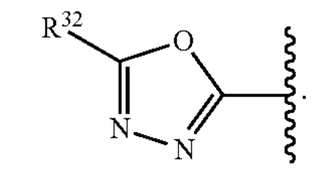
In certain embodiments, R^{33} is a single bond connecting R^3 to the isoquinoline ring, i.e., R^3 has the following formula:



In some embodiments, R^3 is



In some embodiments, R^3 is



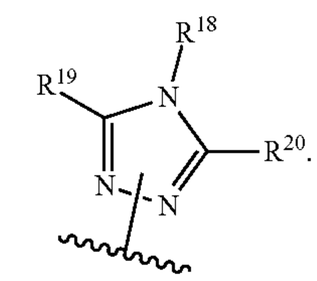
In some embodiments, R^{32} is selected from the group consisting of H, halide, unsubstituted —(C_{1-2} alkyl), unsubstituted —(C_{1-2}haloalkyl), and —$N(R^{53})_2$.

In some embodiments, R^{32} is selected from the group consisting of H, F, methyl, —CF_3, —NHMe, and —NMe_2.

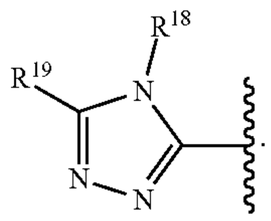
In some embodiments, R^{32} is selected from the group consisting of H and methyl.

In some embodiments, R^{32} is methyl.

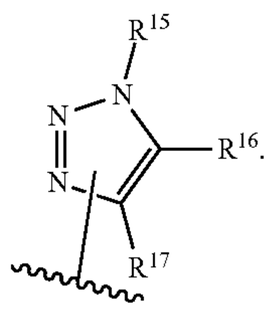
In some embodiments, R^3 is



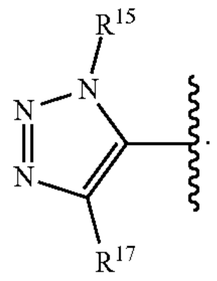
In certain embodiments, R^{20} is a single bond connecting R^3 to the isoquinoline ring, i.e., R^3 has the following formula:



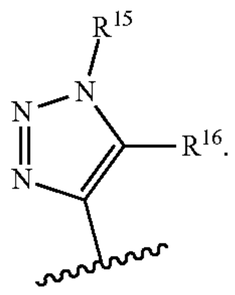
In some embodiments, R^3 is



In certain embodiments, R^{16} is a single bond connecting R^3 to the isoquinoline ring, i.e., R^3 has the following formula:



In certain embodiments, R^{17} is a single bond connecting R^3 to the isoquinoline ring, i.e., R^3 has the following formula:



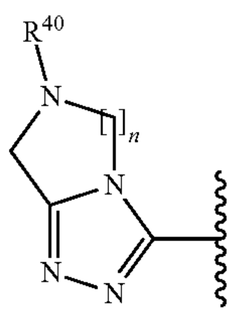
In some embodiments, R^{15} is selected from the group consisting of H and unsubstituted —(C_{1-2} alkyl).

In some embodiments, R^{15} is selected from the group consisting of H and methyl.

In some embodiments, R^{15} is methyl.

In some embodiments, R^{15} is —CD_3.

In some embodiments, R^3 is



and n is 1 to 3.

In some embodiments, R^{18} is selected from the group consisting of H, unsubstituted —(C_{1-3} alkyl), unsubstituted —(C_{1-2} haloalkyl), and —(C_{3-4} carbocyclyl) optionally substituted with 1-2 R^{39}.

In some embodiments, R^{18} is selected from the group consisting of H, methyl, —CF_3, and cyclopropyl optionally substituted with 1-2 R^{39}.

In some embodiments, R^{18} is selected from the group consisting of H and methyl.

In some embodiments, R^{19} is selected from the group consisting of H, halide, unsubstituted —(C_{1-2} alkyl), and unsubstituted —(C_{1-2} haloalkyl).

In some embodiments, R^{19} is selected from the group consisting of H, F, methyl, and —CF_3.

In some embodiments, R^{39} is selected from the group consisting of halide, unsubstituted —(C_{1-3} alkyl), and unsubstituted —(C_{1-2} haloalkyl).

In some embodiments, R^{39} is selected from the group consisting of F, methyl, and —CF_3.

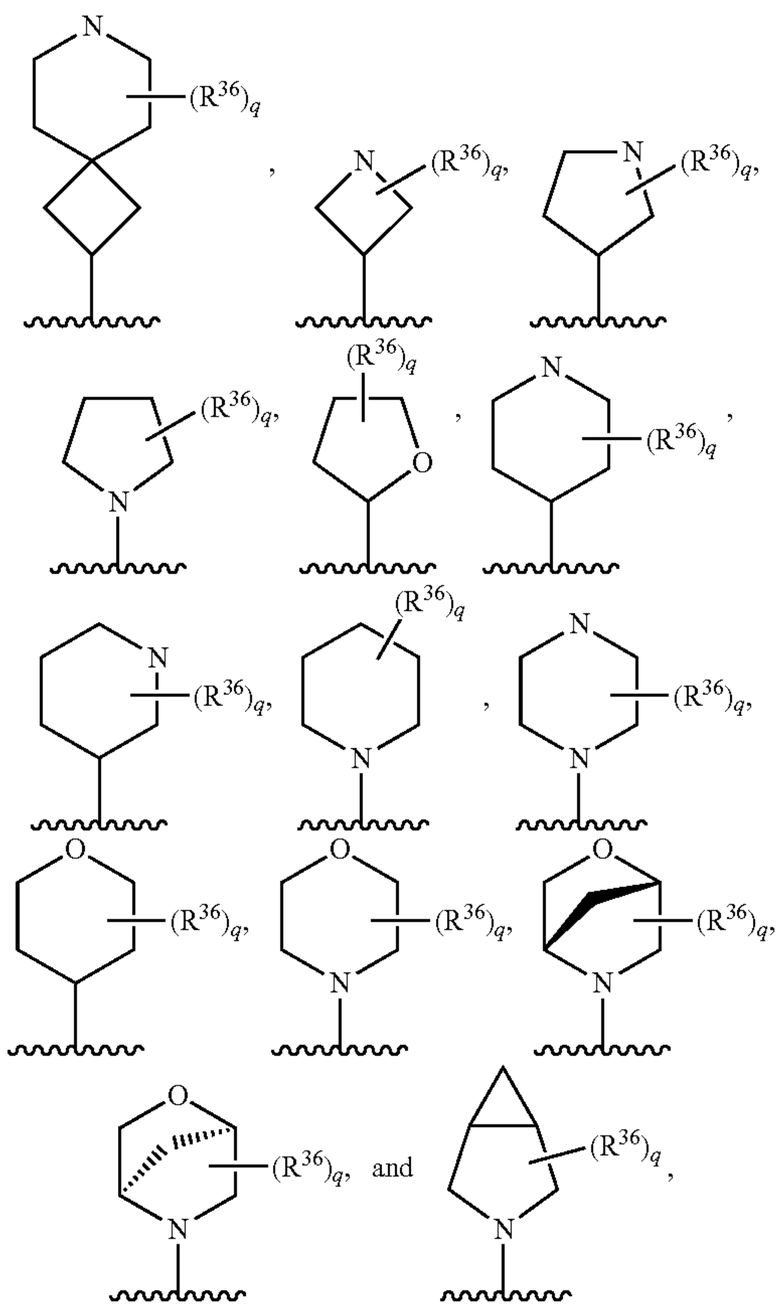
In some embodiments, R^{40} is selected from the group consisting of H and unsubstituted —(C_{1-2} alkyl).

In some embodiments, R^{40} is selected from the group consisting of H and methyl.

In some embodiments, R^6 is selected from the group consisting of —(C_{1-4} alkylene)$_p$heterocyclyl optionally substituted with 1-10 R^{36}, and —(C_{1-4} alkylene)$_p$carbocyclyl optionally substituted with 1-12 R^{37}.

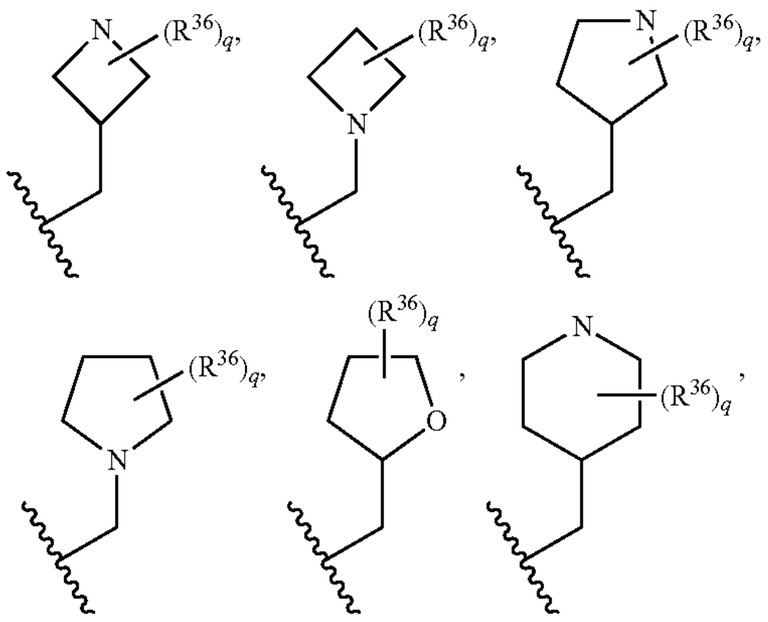
In some embodiments, R^6 is a heterocyclyl optionally substituted with 1-2 R^{36}.

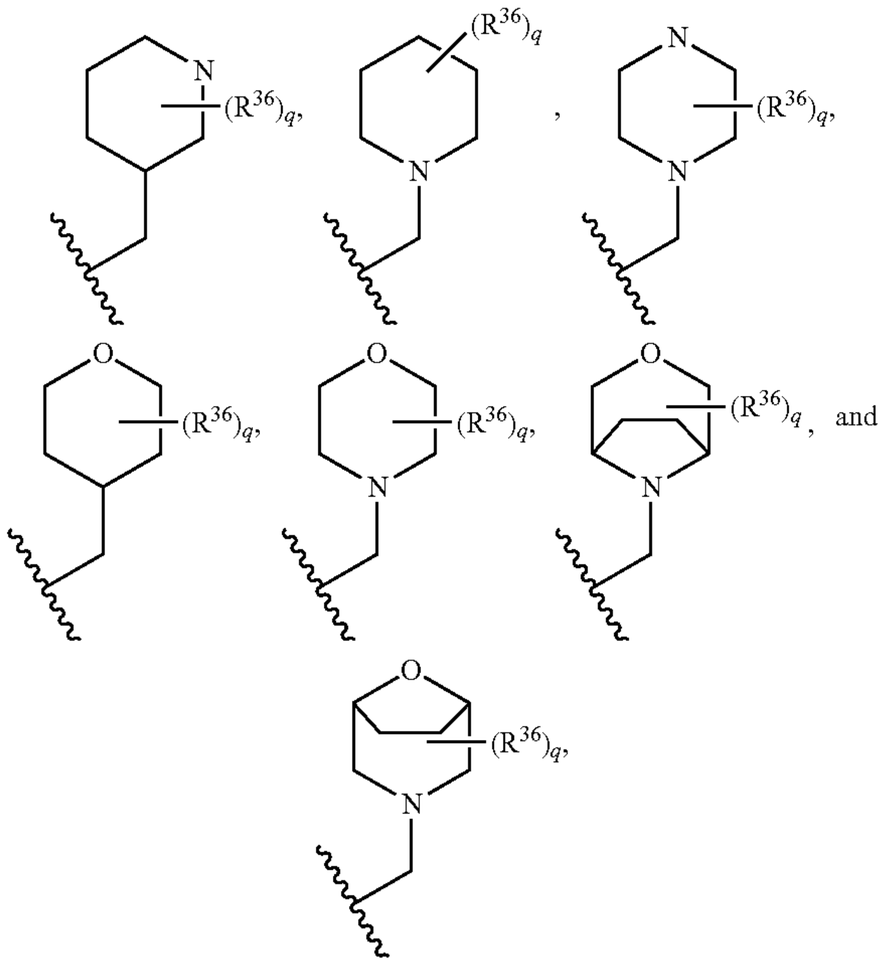
In some embodiments, R^6 is selected from the group consisting of:



and q is 0 to 2.

In some embodiments, R^6 is selected from the group consisting of:





and q is 0 to 2.

In some embodiments, R^6 is a -carbocyclyl optionally substituted with 1-2 R^{37}.

In some embodiments, R^6 is a —(CH_2)carbocyclyl optionally substituted with 1-2 R^{37}.

In some embodiments, R^6 is a —(C_{1-4}alkylene)N(R^{46})(R^{47}).

In some embodiments, R^6 is a —(CH_2)N(R^{46})(R^{47}).

In some embodiments, R^6 is a —(CH_2)NH(C_{1-5}alkyl).

In some embodiments, R^6 is a —(CH_2)NH(C_{1-4}alkyl).

In some embodiments, R^6 is a —(CH_2)NH(C_{1-3}alkyl).

In some embodiments, R^6 is a —(CH_2)NHEt.

In some embodiments, R^6 is a —(CH_2)NHMe.

In some embodiments, R^6 is a —(CH_2)NHcarbocyclyl.

In some embodiments, R^6 is a —(CH_2)NH(CH_2)carbocyclyl.

In some embodiments, R^6 is a —(CH_2)N(C_{1-5} alkyl)$_2$.

In some embodiments, R^6 is a —(CH_2)N(C_{1-4}alkyl)$_2$.

In some embodiments, R^6 is a —(CH_2)N(C_{1-3}alkyl)$_2$.

In some embodiments, R^6 is a —(CH_2)N(C_{1-2}alkyl)$_2$.

In some embodiments, R^6 is a —(CH_2)NMe_2.

In some embodiments, R^6 is a —(CH_2)N(C_{1-5} alkyl)carbocyclyl.

In some embodiments, R^6 is a —(CH_2)N(C_{1-5} alkyl)(CH_2)carbocyclyl.

In some embodiments, R^6 is a —(CH_2)N(C_{1-4}alkyl)carbocyclyl.

In some embodiments, R^6 is a —(CH_2)N(C_{1-4}alkyl)(CH_2)carbocyclyl.

In some embodiments, R^6 is a —(CH_2)N(C_{1-3}alkyl)carbocyclyl.

In some embodiments, R^6 is a —(CH_2)N(C_{1-3}alkyl)(CH_2)carbocyclyl.

In some embodiments, R^6 is a —(CH_2)N(C_{1-2}alkyl)carbocyclyl.

In some embodiments, R^6 is a —(CH_2)N(C_{1-2}alkyl)(CH_2)carbocyclyl.

In some embodiments, R^6 is a —(CH_2)N(Me)carbocyclyl.

In some embodiments, R^6 is a —(CH_2)NMe(CH_2)carbocyclyl.

In some embodiments, R^6 is —CF(C_{1-9}alkyl)$_2$; wherein each alkyl of —CF(C_{1-9} alkyl)$_2$ is, independently, optionally substituted with one or more halides.

In some embodiments, R^6 is —CF(C_{1-9}alkyl)$_2$; wherein each alkyl of —CF(C_{1-9} alkyl)$_2$ is, independently, optionally substituted with one or more fluorines.

In some embodiments, R^6 is —CF(C_{1-7}alkyl)$_2$.

In some embodiments, R^6 is —CF(C_{1-5}alkyl)$_2$.

In some embodiments, R^6 is —CF(C_{1-4}alkyl)$_2$.

In some embodiments, R^6 is —CF(C_{1-3}alkyl)$_2$.

In some embodiments, R^6 is —CF(C_{1-2}alkyl)$_2$.

In some embodiments, R^6 is —$CFMe_2$.

In some embodiments, R^6 is —CF(Me)(Et).

In some embodiments, R^6 is —$CFEt_2$.

In some embodiments, R^6 is —CF(Et)(^{n}Pr).

In some embodiments, R^6 is —CF^{n}Pr$_2$.

In some embodiments, R^6 is —CF(Me)(^{n}Pr).

In some embodiments, R^6 is —CF^{i}Pr$_2$.

In some embodiments, R^6 is —CF(Et)(^{i}Pr).

In some embodiments, R^6 is —CF(Me)(^{i}Pr).

In some embodiments, R^{36} is selected from the group consisting of halide, unsubstituted —(C_{1-5} alkyl), unsubstituted —(C_{1-5} haloalkyl), —(CH_2CH_2)OR^{42}, heterocyclyl optionally substituted with 1-2 R^{43}, —(CH_2)heterocyclyl optionally substituted with 1-2 R^{43}, —(C_{3-4} carbocyclyl) optionally substituted with 1-2 R^{44}, and —(CH_2)(C_{3-4} carbocyclyl) optionally substituted with 1-2 R^{44}.

In some embodiments, R^{37} is selected from the group consisting of halide, unsubstituted —(C_{1-5} alkyl), unsubstituted —(C_{1-5} haloalkyl), heterocyclyl optionally substituted with 1-2 R^{43}, and —(CH_2)heterocyclyl optionally substituted with 1-2 R^{43}.

In some embodiments, the heterocyclyl is selected from the group consisting of azetidinyl, oxetanyl, pyrrolidinyl, tetrahydrofuranyl, piperidinyl, piperazinyl, morpholinyl, and tetrahydropyranyl.

In some embodiments, R^{42} is selected from the group consisting of unsubstituted —(C_{1-3} alkyl), and unsubstituted —(C_{1-3} haloalkyl).

In some embodiments, R^{42} is selected from the group consisting of methyl, ethyl, propyl, isopropyl, —CF_3.

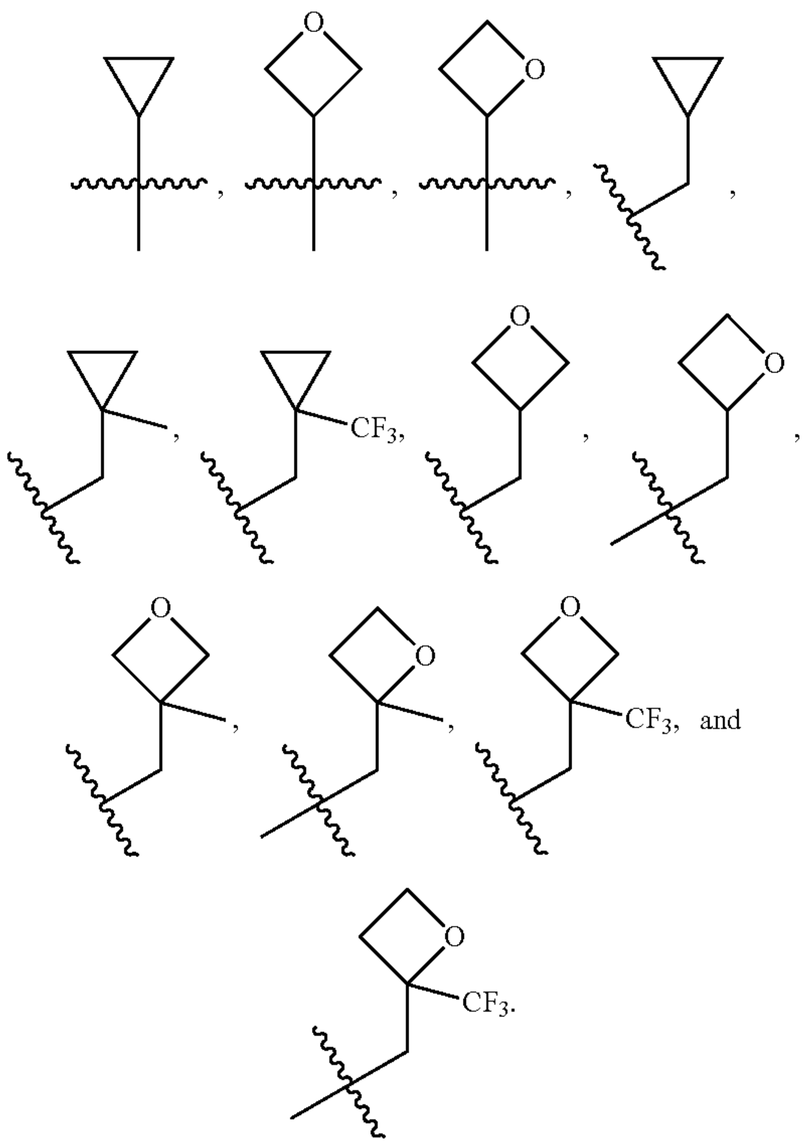
In some embodiments, R^{43} is selected from the group consisting of halide, unsubstituted —(C_{1-2} alkyl), and unsubstituted —(C_{1-2} haloalkyl).

In some embodiments, R^{43} is selected from the group consisting of F, methyl, ethyl, —CF_3.

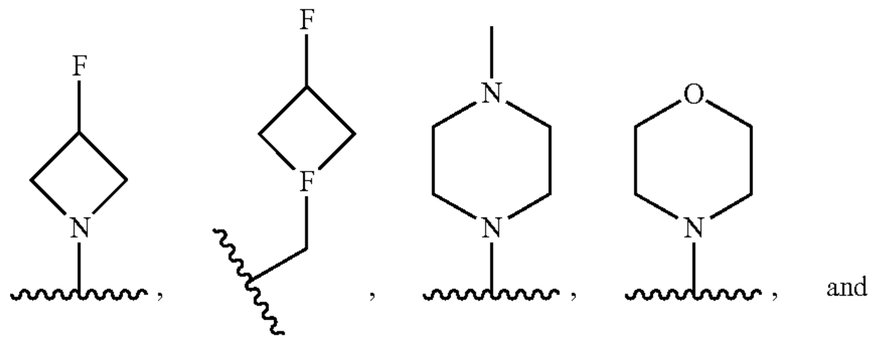
In some embodiments, R^{44} is selected from the group consisting of halide, unsubstituted —(C_{1-2} alkyl), and unsubstituted —(C_{1-2} haloalkyl).

In some embodiments, R^{44} is selected from the group consisting of F, methyl, ethyl, —CF_3.

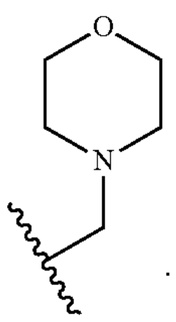
In some embodiments, R^{36} is selected from the group consisting of F, methyl, ethyl, n-propyl, isopropyl, isobutyl, tert-butyl, neopentyl, —CH_2CH_2F, —CH_2CHF_2, —CH_2CF_3, —$CH_2CF_2CH_3$, —$CH_2C(CH_3)_2F$, —$CH_2CH_2CF_3$, —$(CH_2CH_2)O(C_{1\text{-}3}$ alkyl),



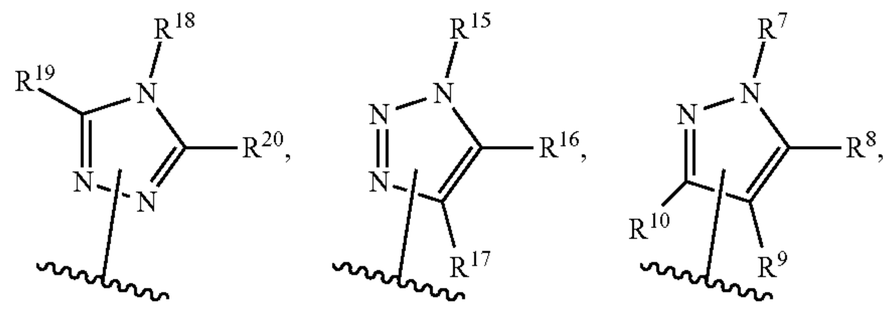
In some embodiments, R^{37} is selected from the group consisting of F, methyl, ethyl, —CF_3, —OCF_3, —OMe,



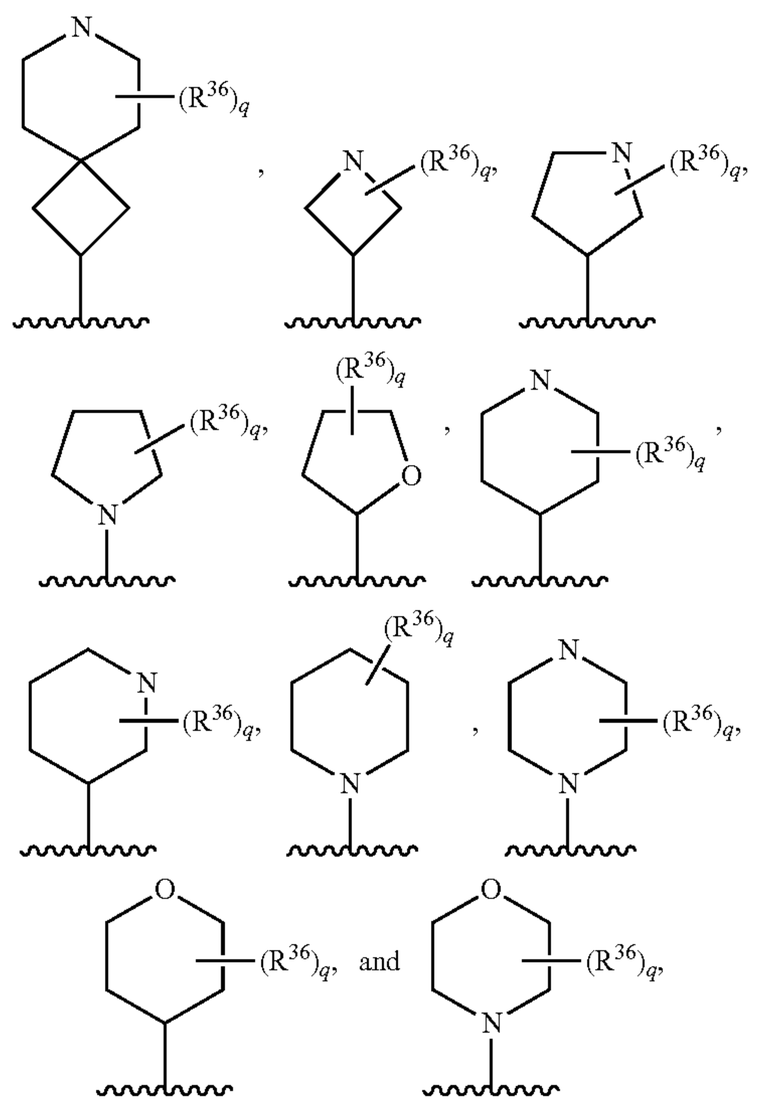
In some embodiments, R^3 is selected from the group consisting of:



In some embodiments, R^3 is selected from the group consisting of:

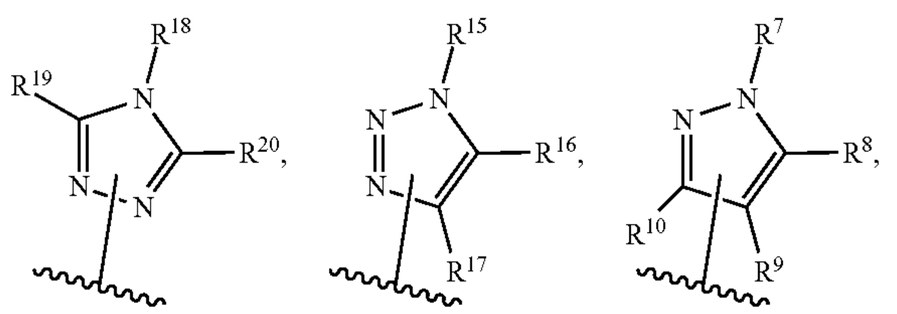


where in X is S or O and R^6 is selected from the group consisting of:



and q is 0 to 2.

In some embodiments, R^3 is selected from the group consisting of:



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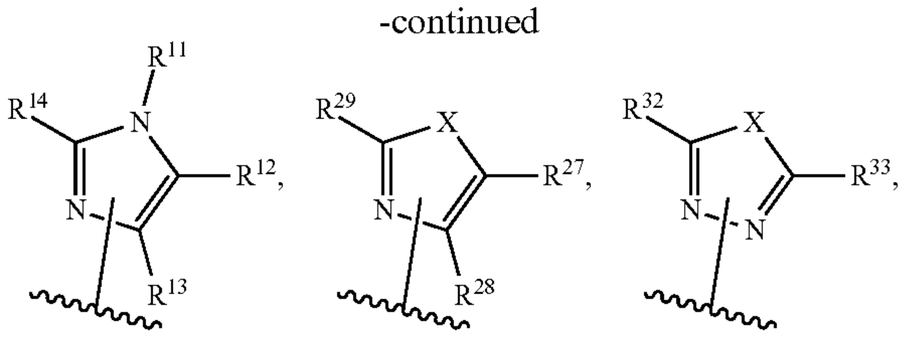
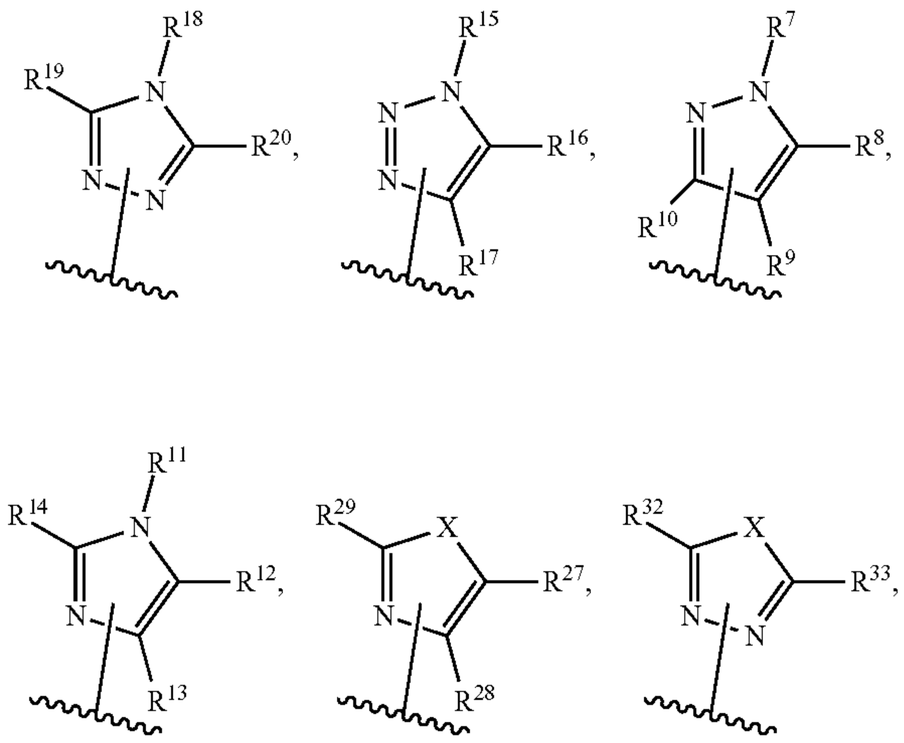


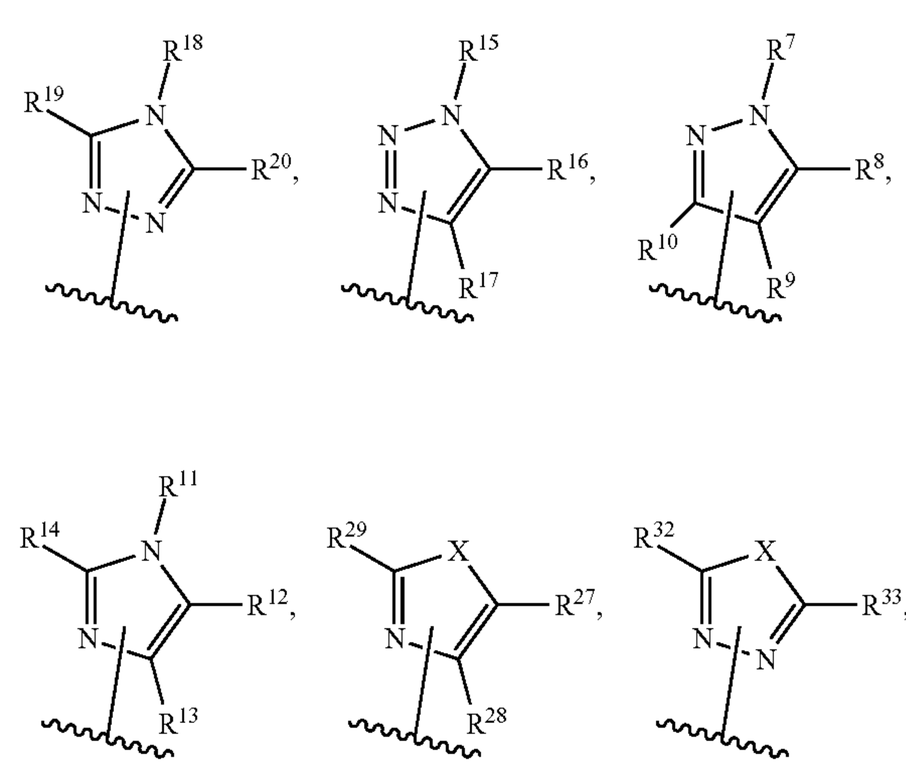
where in X is S or O and R^6 is selected from the group consisting of -carbocyclyl optionally substituted with 1-2 R^{37} and —(CH_2)carbocyclyl optionally substituted with 1-2 R^{37}.

In some embodiments, R^3 is selected from the group consisting of:

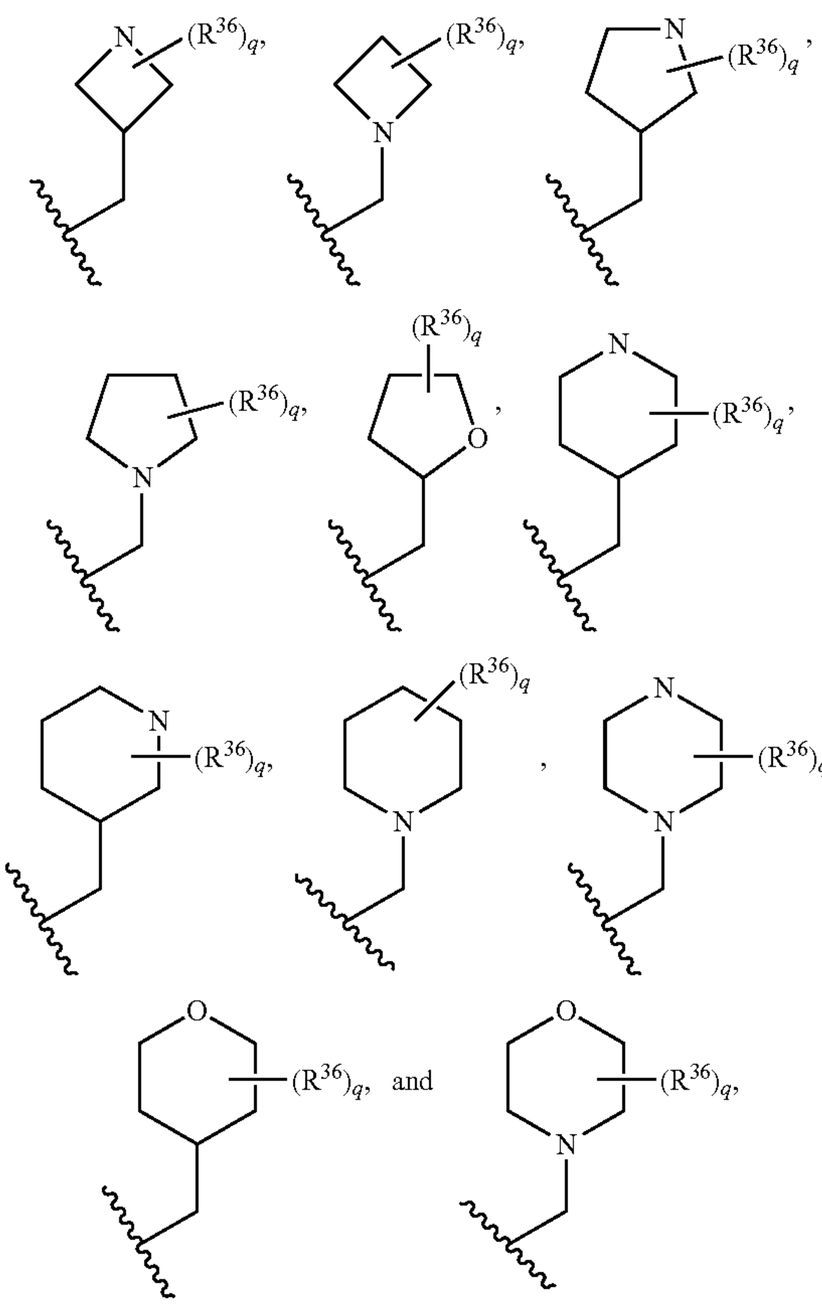


where in X is S or O and R^6 is —$CF(C_{1\text{-}9}\ alkyl)_2$; wherein the alkyl of —$CF(C_{1\text{-}9}\ alkyl)_2$ is optionally substituted with one or more halides.

In some embodiments, R^3 is selected from the group consisting of:

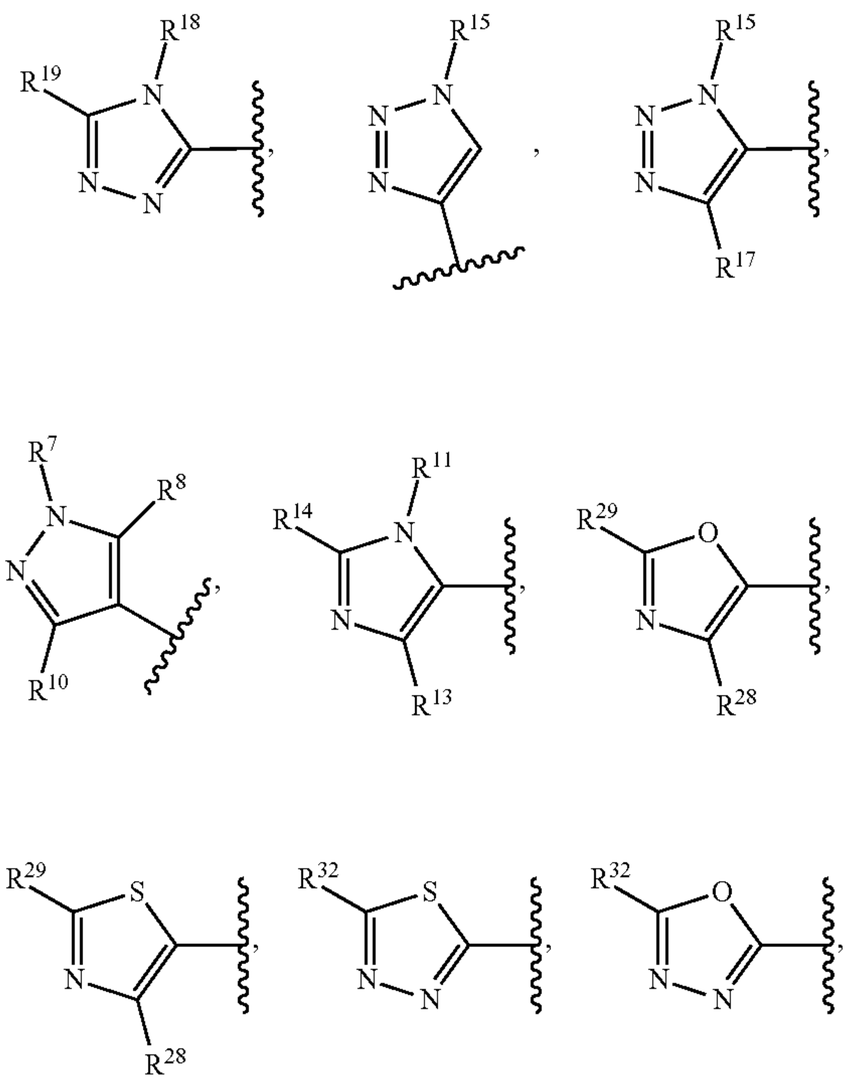


where in X is S or O and R^6 is selected from the group consisting of:

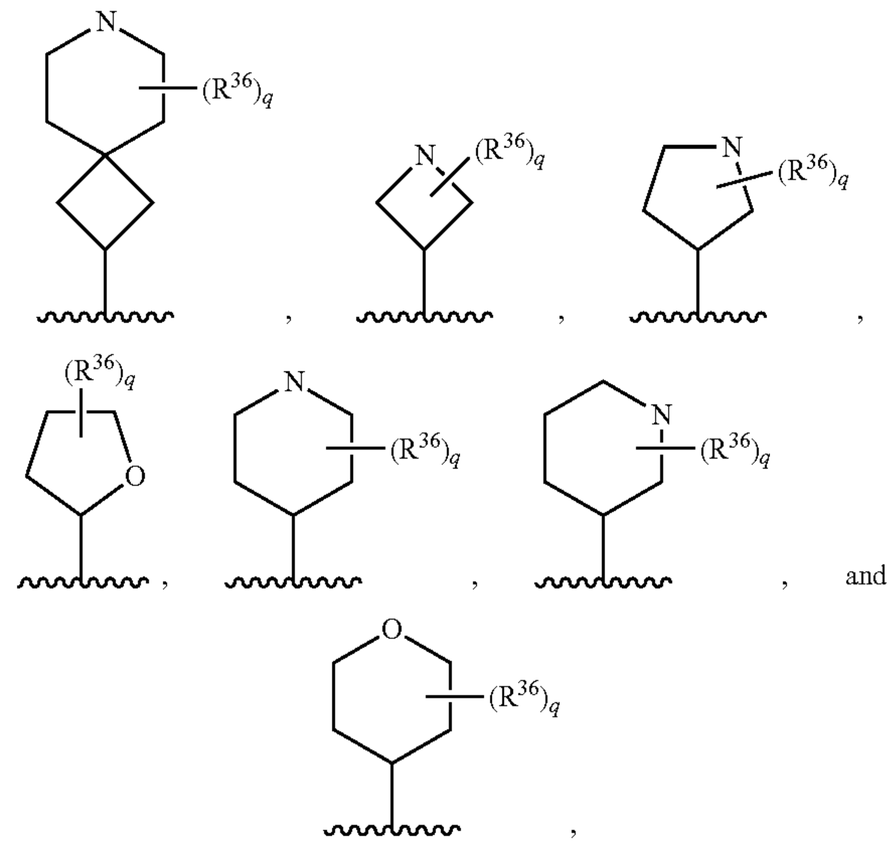


and q is 0 to 2.

In some embodiments, R^3 is selected from the group consisting of:

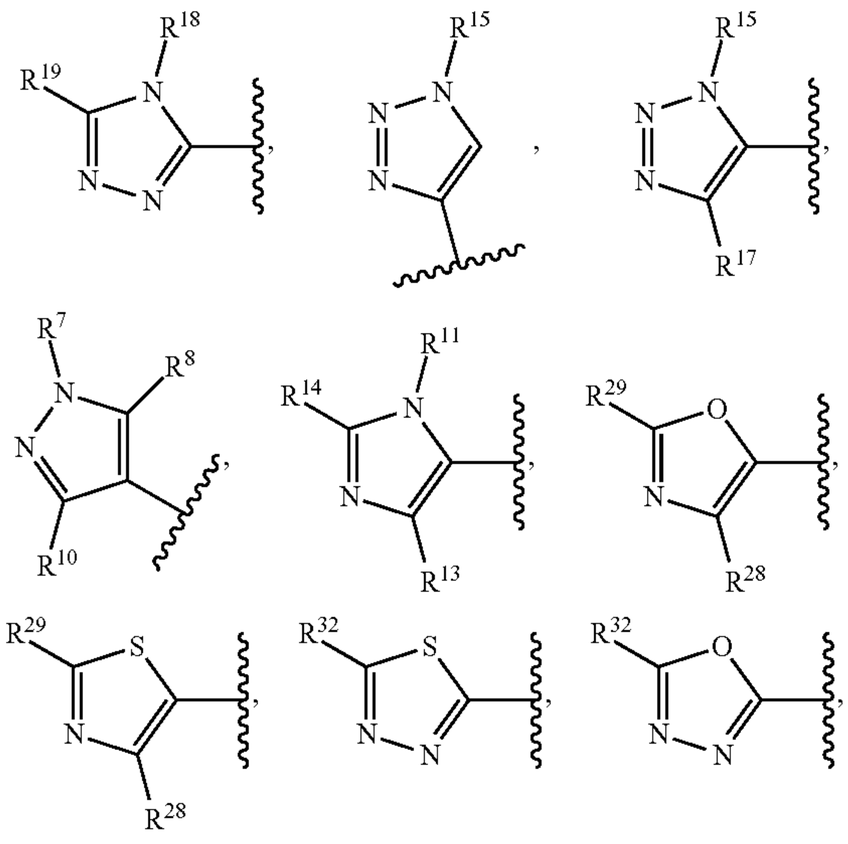


and R^6 is selected from the group consisting of:

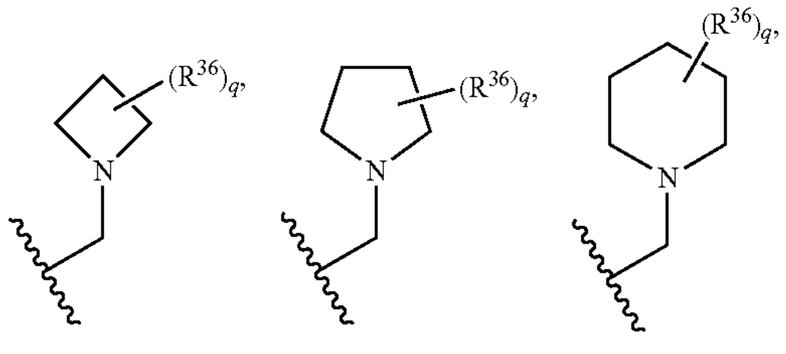


and q is 0 to 2.

In some embodiments, R^3 is selected from the group consisting of:



and R^6 is selected from the group consisting of:



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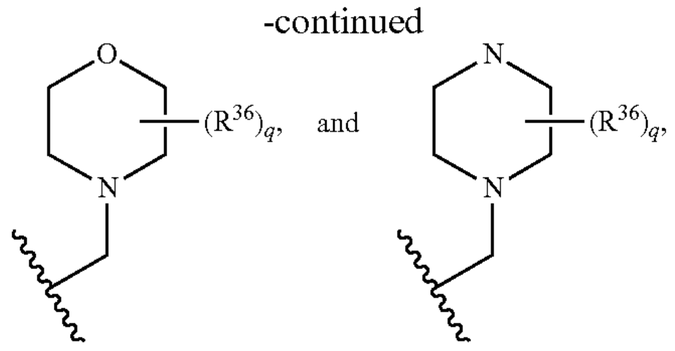
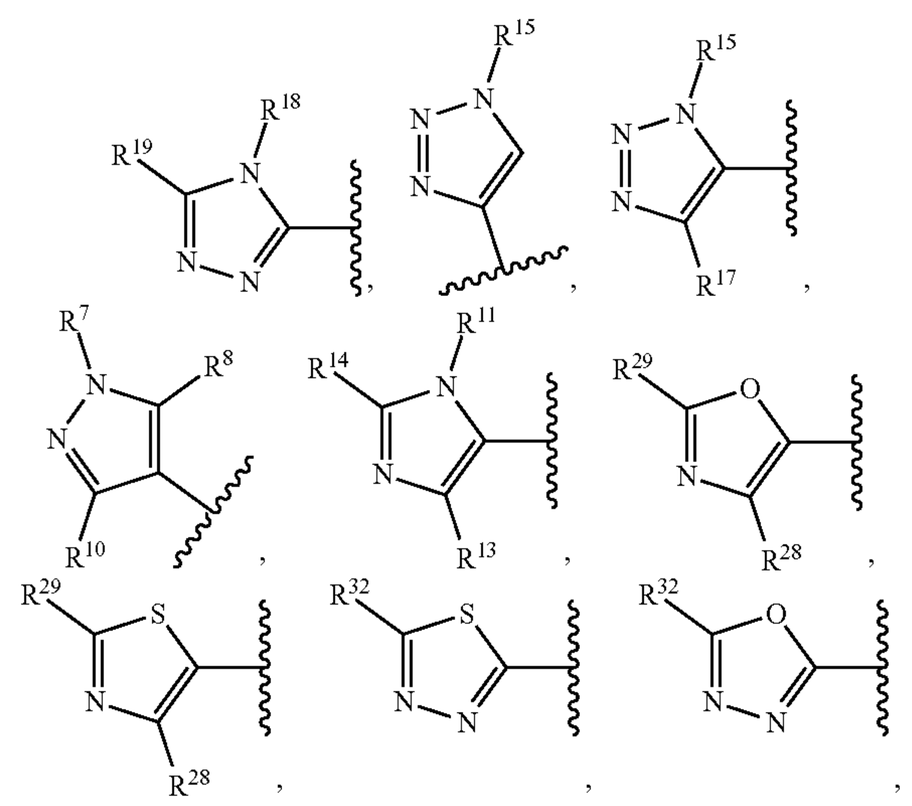


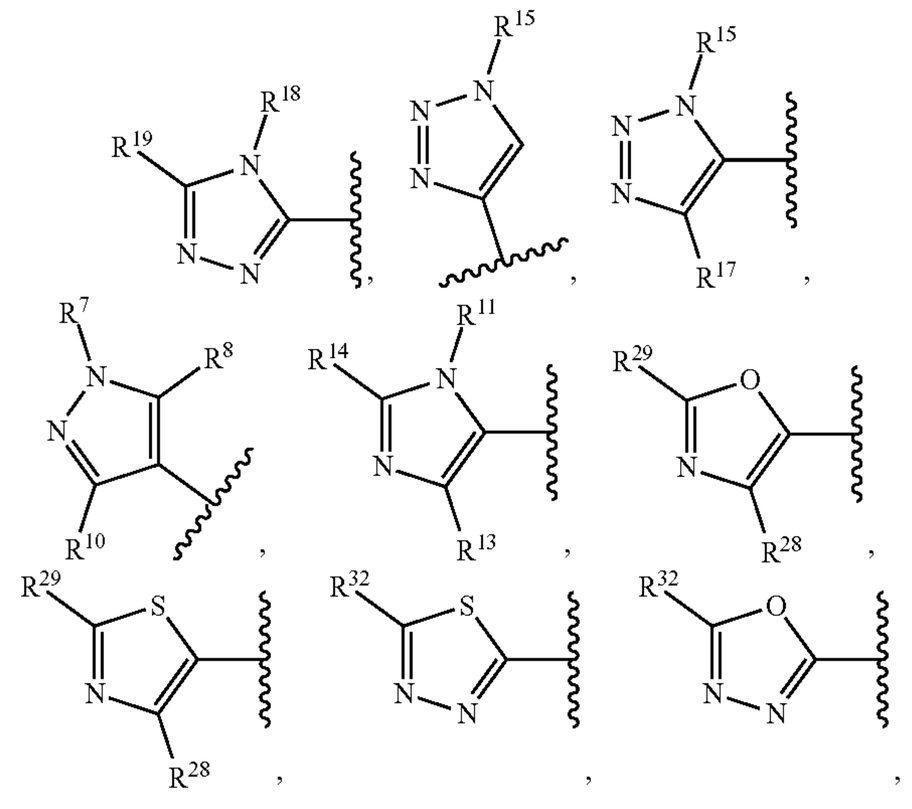
and q is 0 to 2.

In some embodiments, R^3 is selected from the group consisting of:



and R^6 is —$CF(C_{1\text{-}7}alkyl)_2$; wherein the alkyl of —$CF(C_{1\text{-}7}alkyl)_2$ is optionally substituted with one or more fluorines.

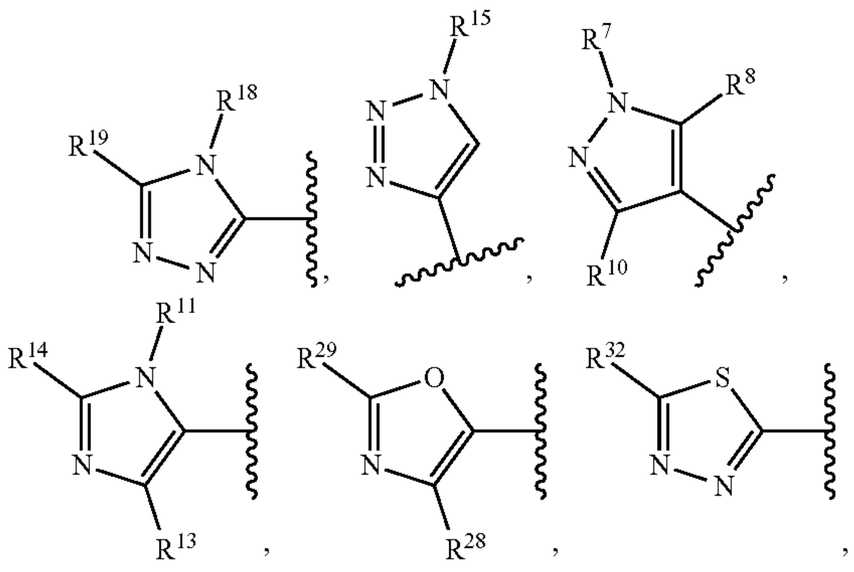
In some embodiments, R^3 is selected from the group consisting of:



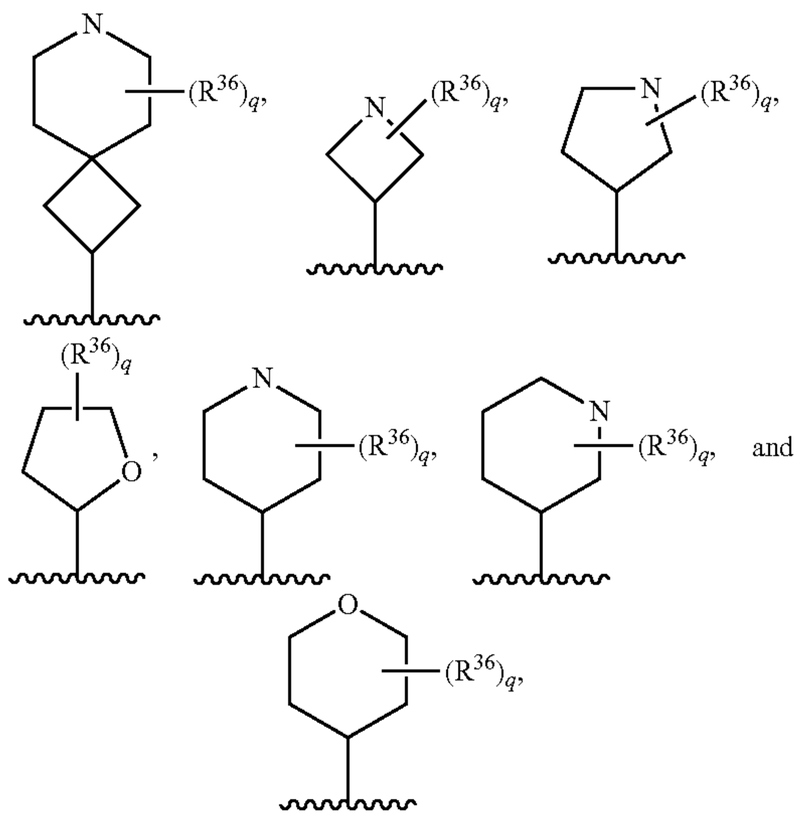
and R^6 is selected from the group consisting of -cyclopropyl, -cyclobutyl, -cyclopentyl, -cyclohexyl each independently optionally substituted with 1-2 R^{37} and —(CH_2)cyclopro-

pyl, —(CH_2)cyclobutyl, —(CH_2)cyclopentyl, and —(CH_2)cyclohexyl, each independently optionally substituted with 1-2 R^{37}.

In some embodiments, R^3 is selected from the group consisting of:

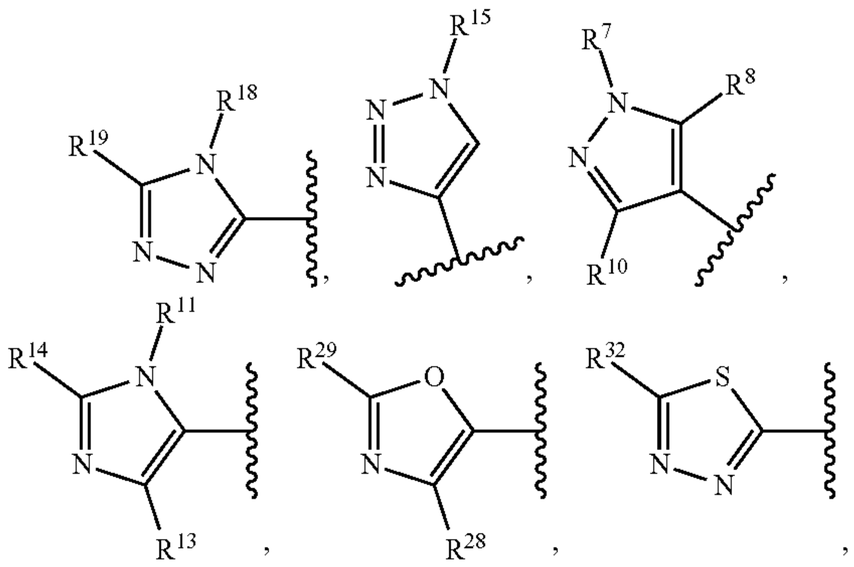


and R^6 is selected from the group consisting of:

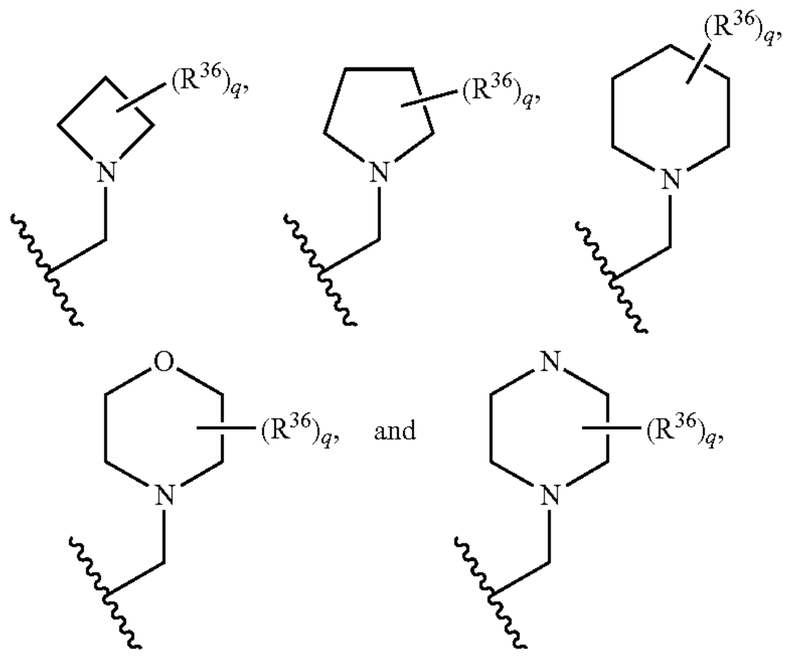


and q is 0 to 2.

In some embodiments, R^3 is selected from the group consisting of:

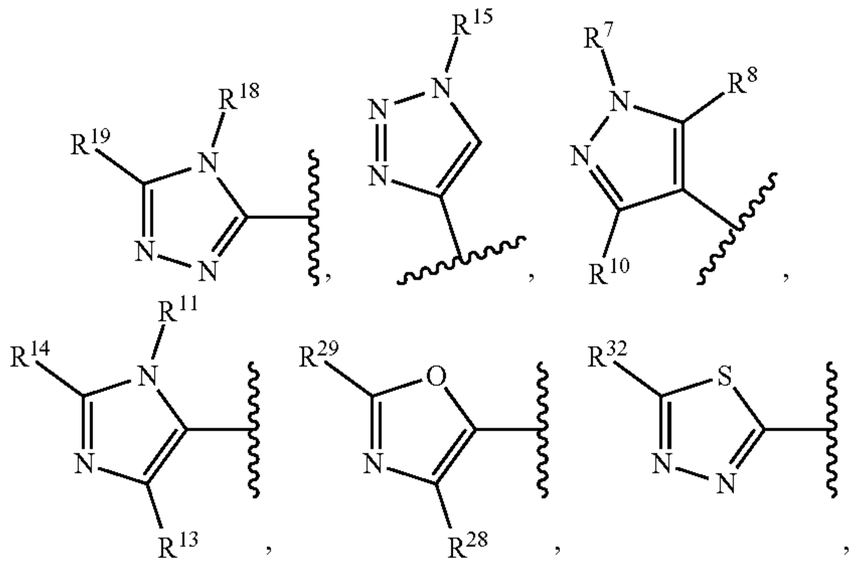


and R^6 is selected from the group consisting of:



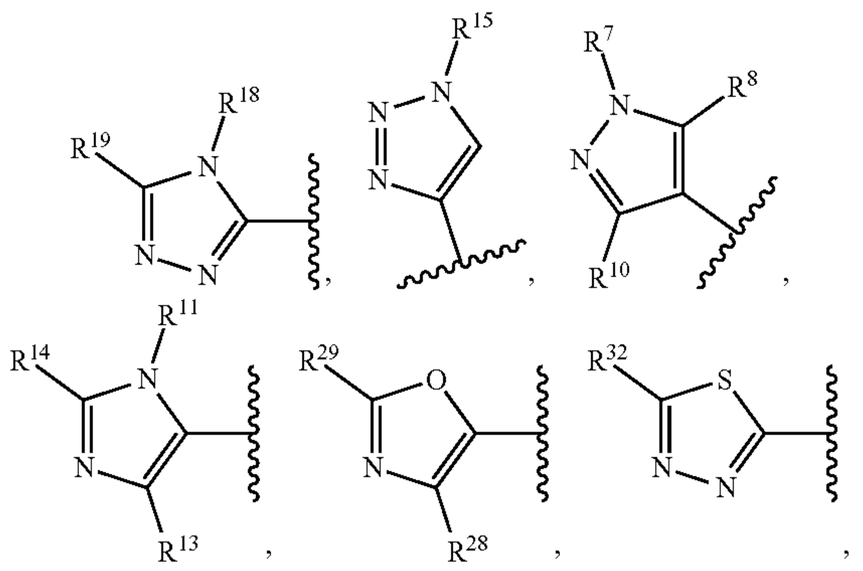
and q is 0 to 2.

In some embodiments, R^3 is selected from the group consisting of:



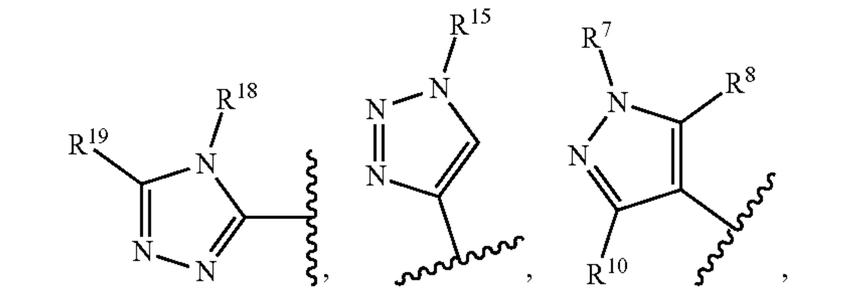
and R^6 is selected from the group consisting of -cyclopropyl, -cyclobutyl, -cyclopentyl, -cyclohexyl each optionally substituted with 1-2 R^{37} and —(CH_2)cyclopropyl, —(CH_2)cyclobutyl, —(CH_2)cyclopentyl, and —(CH_2)cyclohexyl, each optionally substituted with 1-2 R^{37}.

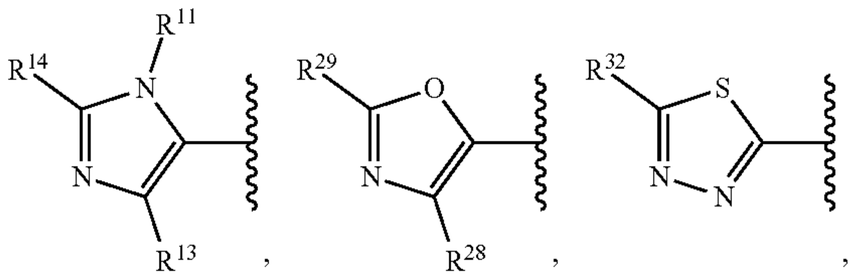
In some embodiments, R^3 is selected from the group consisting of:



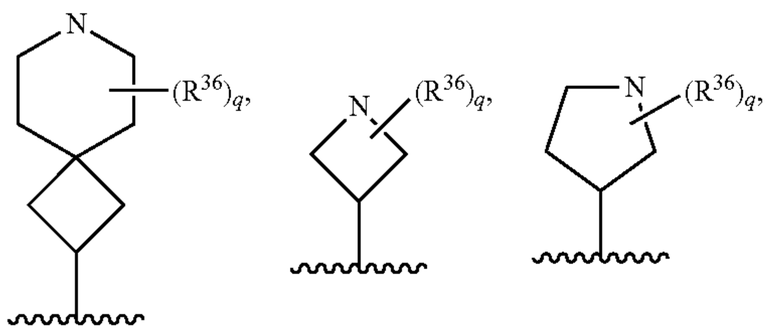
and R^6 is —$CF(C_{1\text{-}5}\ alkyl)_2$; wherein the alkyl of —$CF(C_{1\text{-}5}alkyl)_2$ is optionally substituted with 1-4 fluorines.

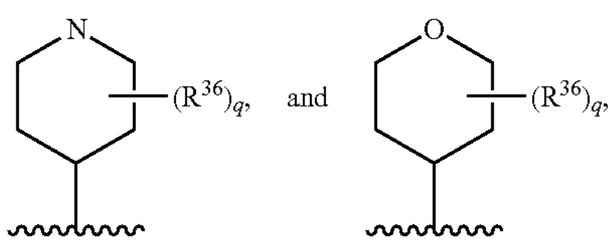
In some embodiments, R^3 is selected from the group consisting of:



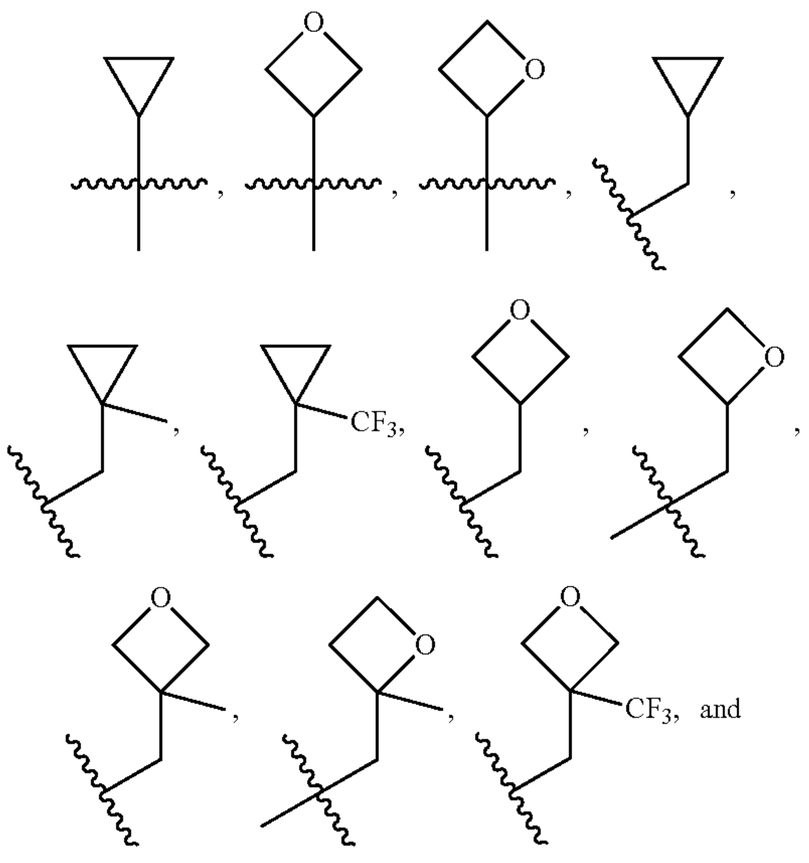


R^6 is selected from the group consisting of:





q is 1; and R^{36} is selected from the group consisting of F, methyl, ethyl, n-propyl, isopropyl, isobutyl, tert-butyl, neopentyl, —CHF_2, —CF_3, —CH_2CH_2F, —CH_2CHF_2, —CH_2CF_3, —$CH_2CF_2CH_3$, —$CH_2C(CH_3)_2F$, —$CH_2CH_2CF_3$, —$(CH_2CH_2)O(C_{1\text{-}3}$ alkyl),



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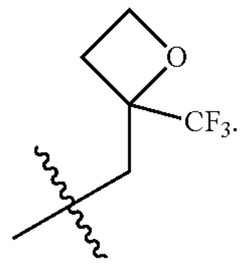
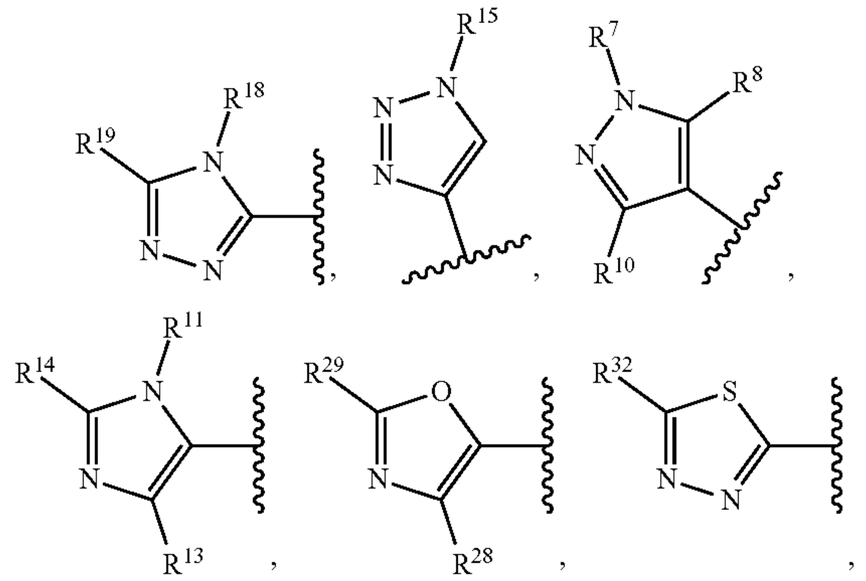
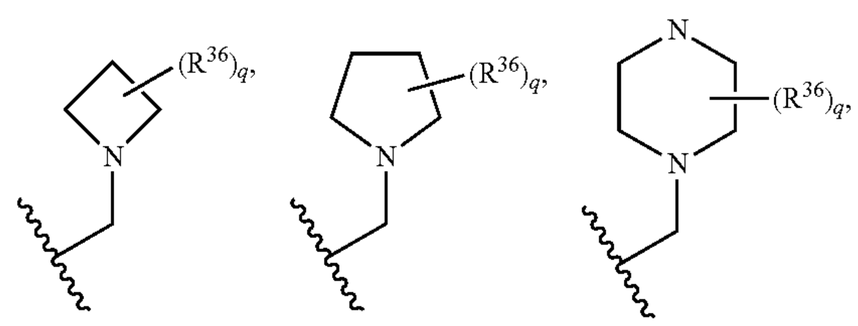


In some embodiments, R^3 is selected from the group consisting of:

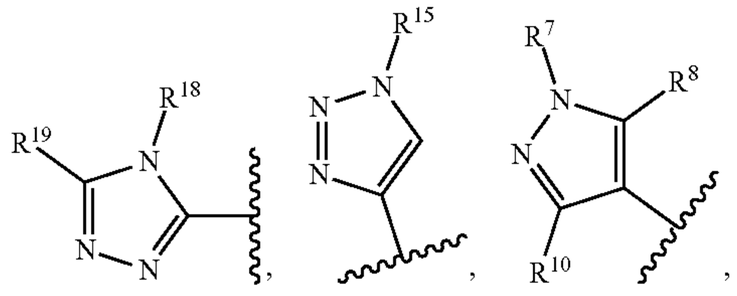


R^6 is selected from the group consisting of:



q is 0 to 2, and each R^{36} is independently selected from the group consisting of F, methyl, and —CF_3.

In some embodiments, R^3 is selected from the group consisting of:



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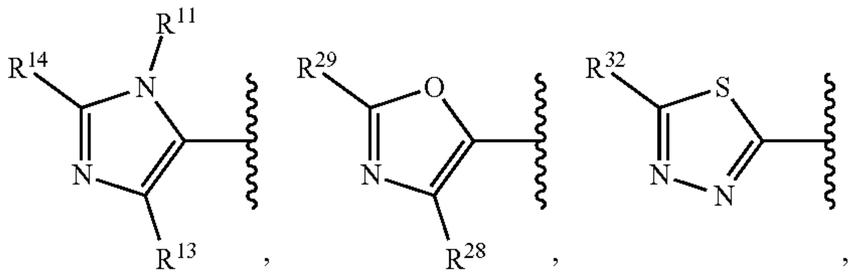
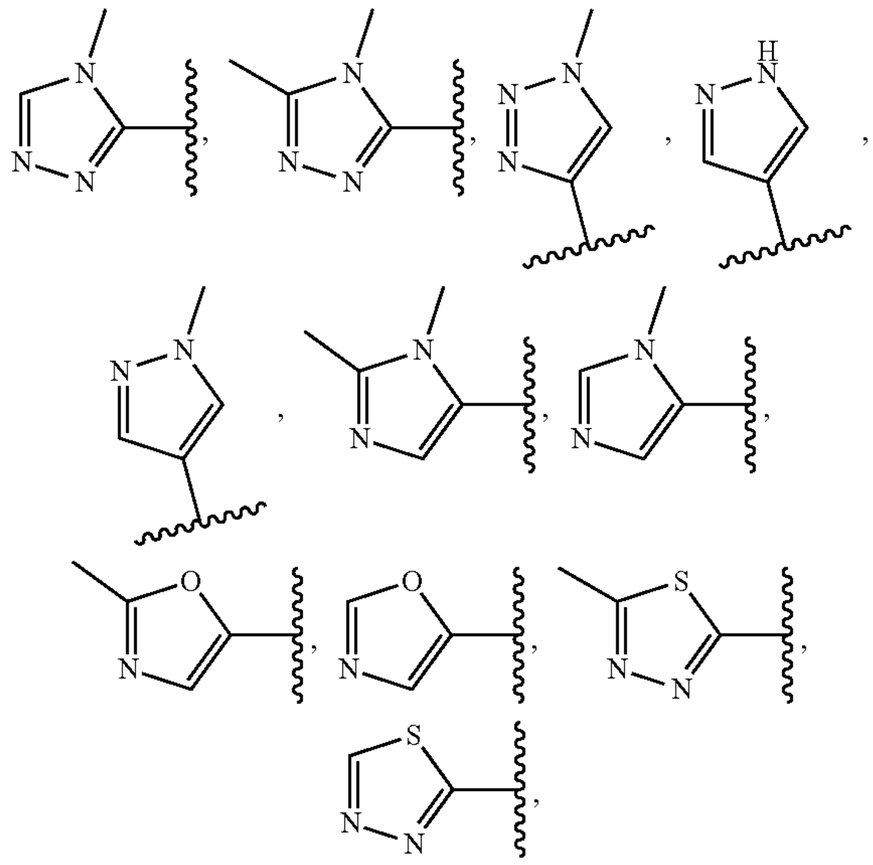
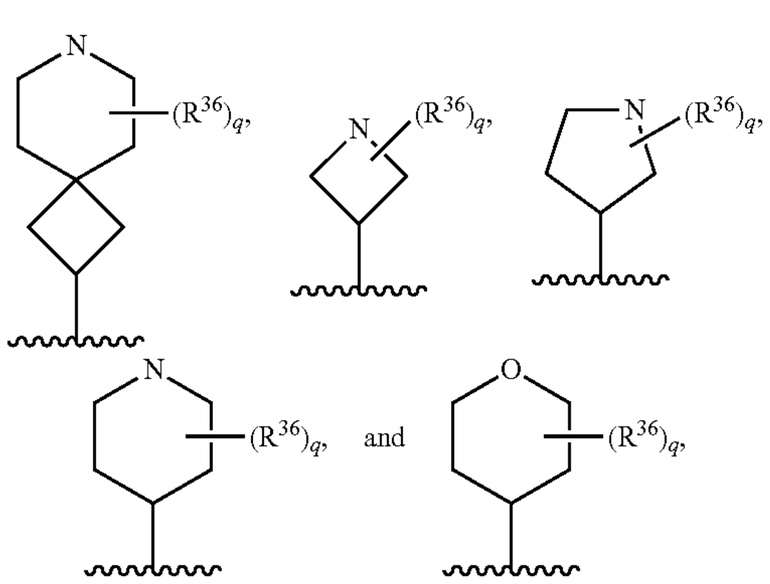


and R^6 is selected from the group consisting of -cyclopropyl, -cyclobutyl, -cyclopentyl, -cyclohexyl each optionally substituted with 1-2 R^{37} and —(CH_2)cyclopropyl, —(CH_2)cyclobutyl, —(CH_2)cyclopentyl, and —(CH_2)cyclohexyl, each optionally substituted with 1-2 R^{37}, and each R^{37} is independently selected from the group consisting of F, methyl, —CF_3, —OCF_3, and —OMe.

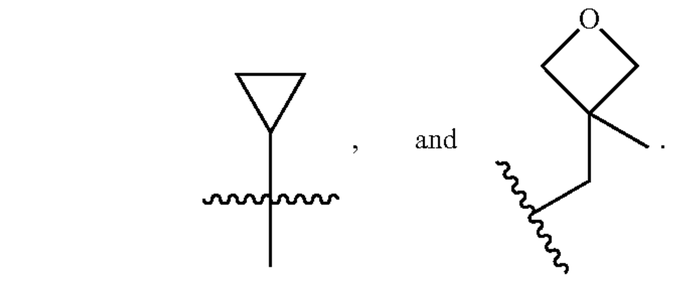
In some embodiments, R^3 is selected from the group consisting of:



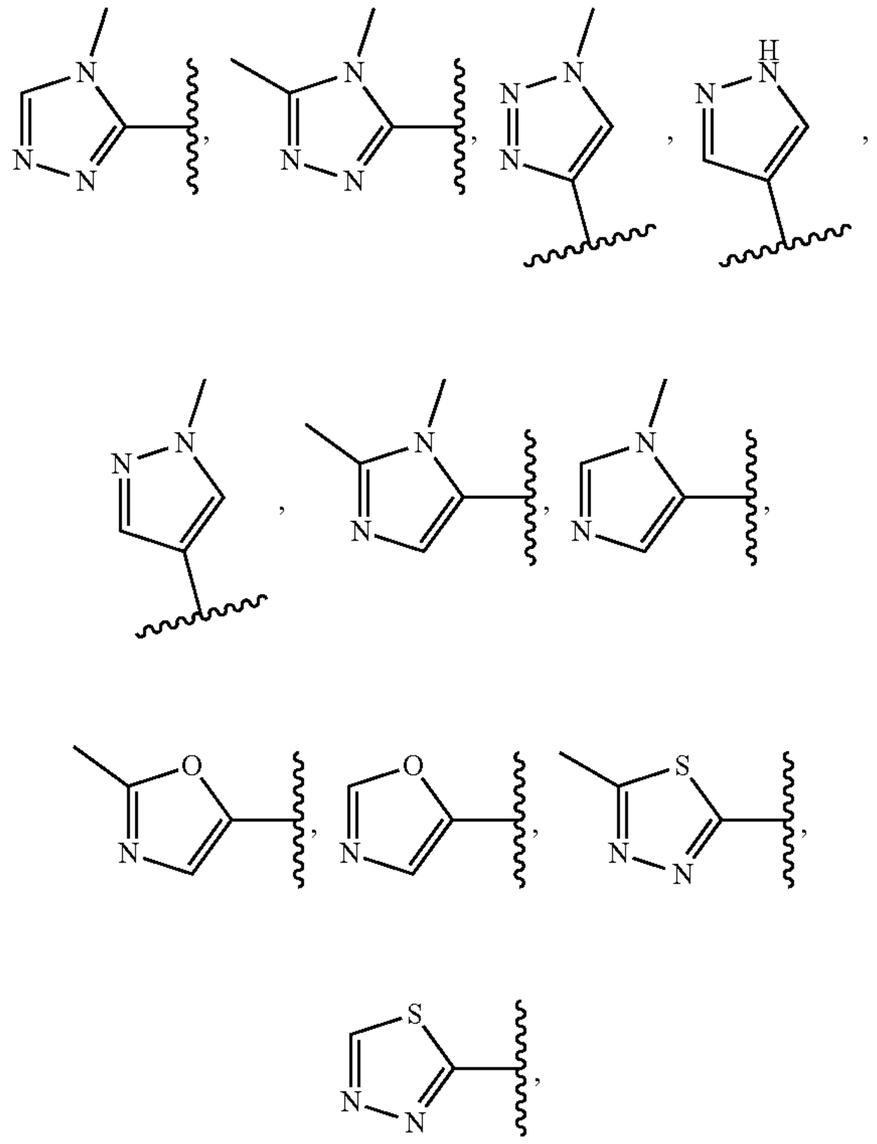
R^6 is selected from the group consisting of:



q is 1; and R^{36} is selected from the group consisting of F, methyl, ethyl, n-propyl, isopropyl, isobutyl, tert-butyl, neopentyl, —CHF_2, —CF_3, —CH_2CH_2F, —CH_2CHF_2, —CH_2CF_3, —$CH_2CF_2CH_3$, —$CH_2C(CH_3)_2F$, —$CH_2CH_2CF_3$, —(CH_2CH_2)O(C_{1-3} alkyl),

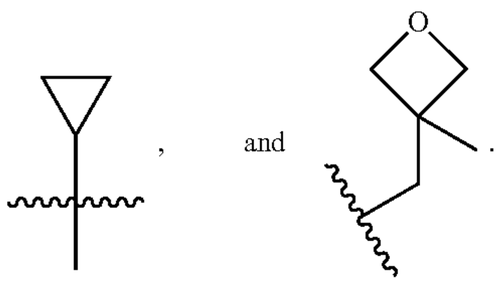


In some embodiments, R^3 is selected from the group consisting of:

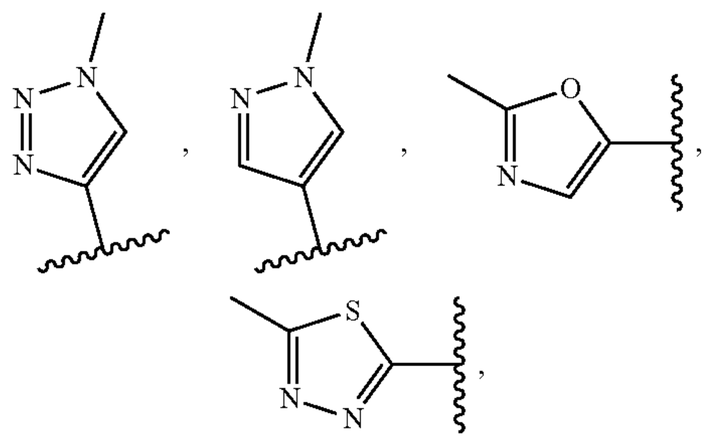


R^6 is selected from the group consisting of:

and R^{36} is selected from the group consisting of methyl, ethyl, isopropyl, isobutyl, —CH_2CH_2F, —CH_2CHF_2, —CH_2CF_3, —$CH_2CF_2CH_3$, —$CH_2C(CH_3)_2F$, —$CH_2CH_2CF_3$, —(CH_2CH_2)OMe, —(CH_2CH_2)OiPr,

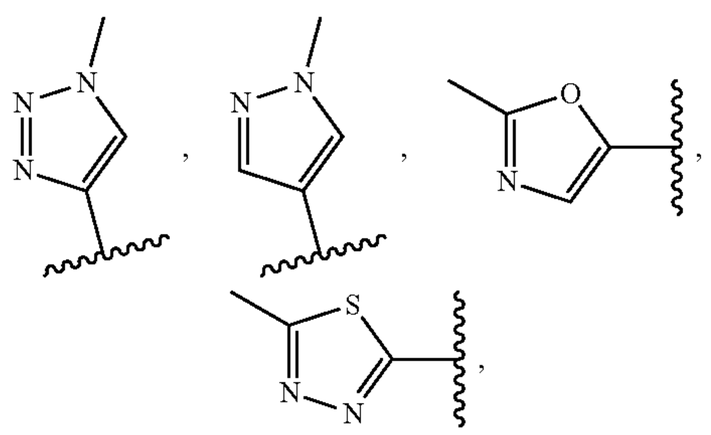


In some embodiments, R^3 is selected from the group consisting of:



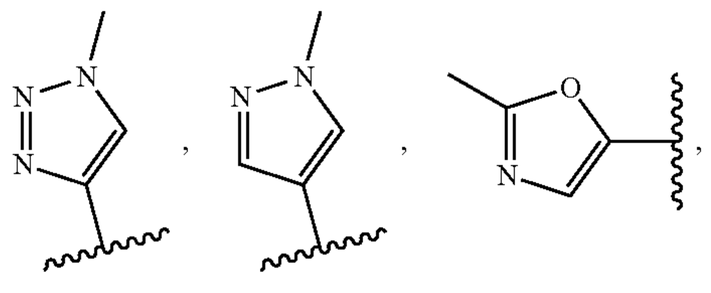
R^6 is selected from the group consisting of —$(C_{1-4}$ alkylene$)_p$heterocyclyl optionally substituted with 1-10 R^{36} and —$(C_{1-4}$ alkylene$)_p$carbocyclyl optionally substituted with 1-12 R^{37}.

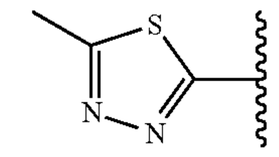
In some embodiments, R^3 is selected from the group consisting of:



R^6 is selected from the group consisting of —(CH_2)heterocyclyl optionally substituted with 1-2 R^{36}-heterocyclyl optionally substituted with 1-2 R^{36}, and -carbocyclyl optionally substituted with 1-2 R^{37}, and R^{36} is selected from the group consisting of halide and unsubstituted —$(C_{1-9}$ alkyl), and R^{37} is selected from the group consisting of halide and unsubstituted —$(C_{1-9}$ alkyl), —$N(R^{53})_2$, and -heterocyclyl optionally substituted with 1-2 R^{43}.

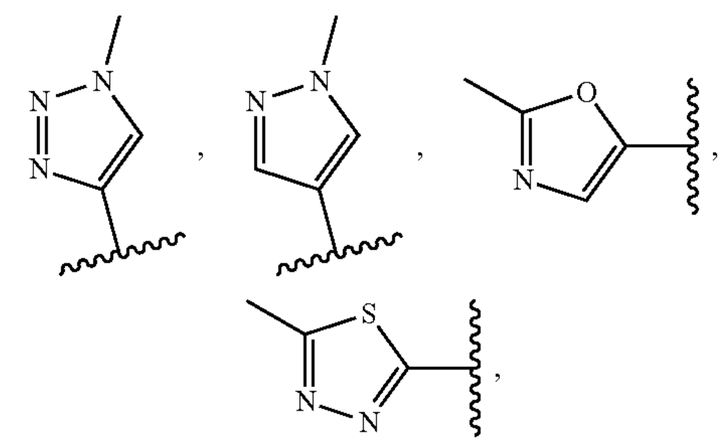
In some embodiments, R^3 is selected from the group consisting of:



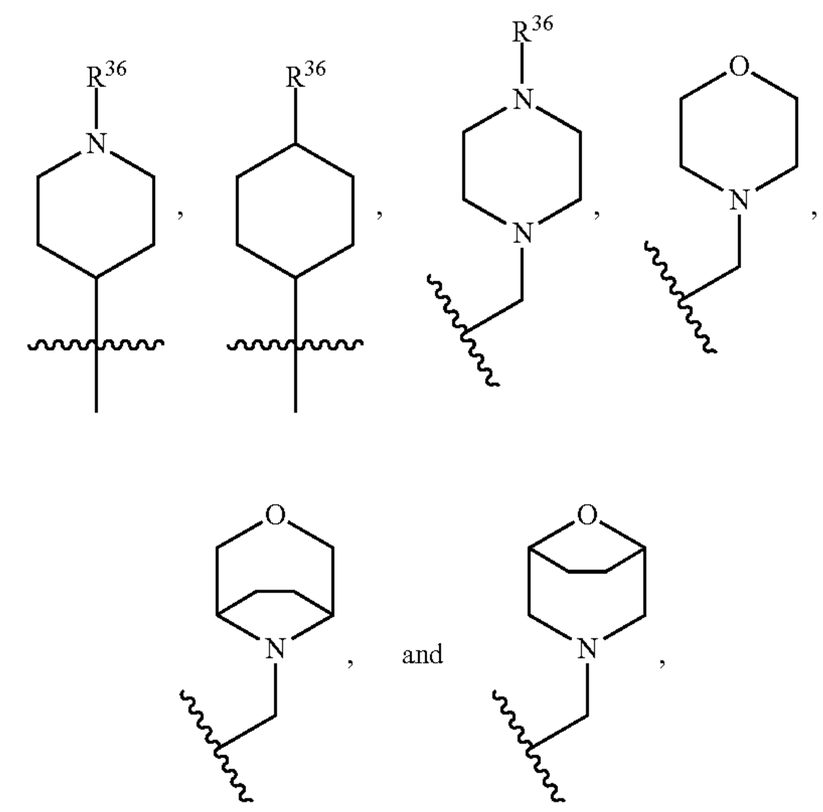


R^6 is selected from the group consisting of —(CH_2)heterocyclyl optionally substituted with 1 R^{36}-heterocyclyl optionally substituted with 1 R^{36}, and -carbocyclyl substituted with 1 R^{37}, and R^{36} is unsubstituted —$(C_{1-5}$ alkyl), and R^{37} is selected from the group consisting of —$N(C_{1-3}$ alkyl$)_2$, and an unsubstituted-heterocyclyl.

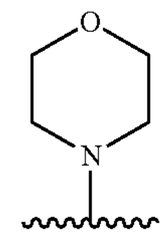
In some embodiments, R^3 is selected from the group consisting of:



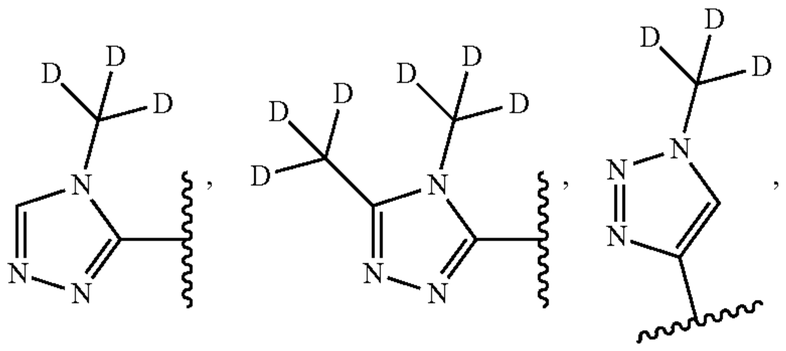
R^6 is selected from the group consisting of:

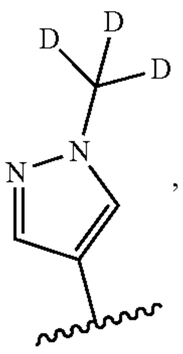


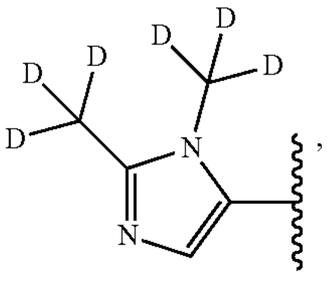
and R^{36} is selected from the group consisting of methyl, ethyl, isopropyl, isobutyl, —NMe_2, and



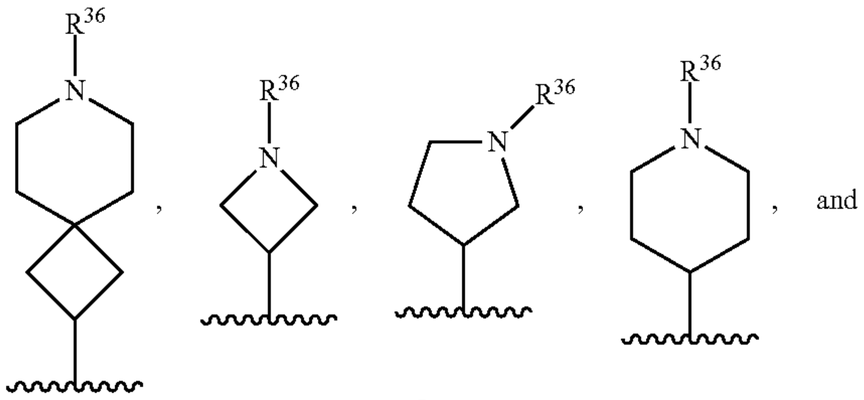
In some embodiments, R^3 is selected from the group consisting of:





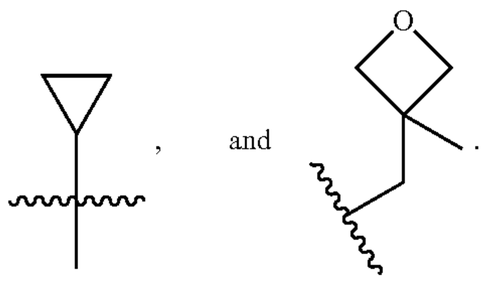


R^6 is selected from the group consisting of:



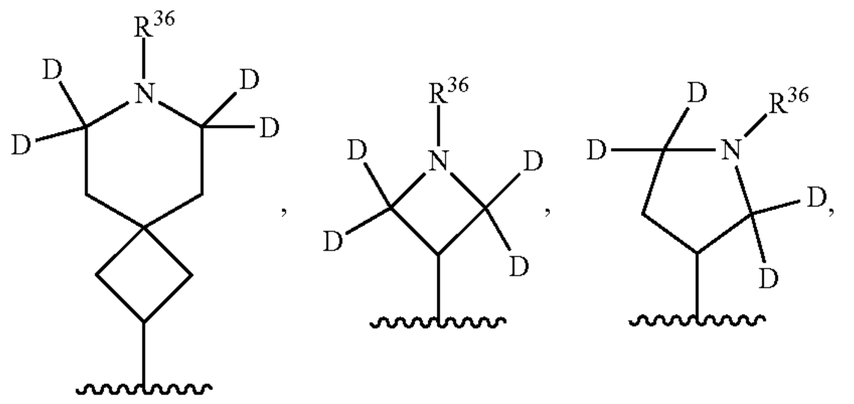
and

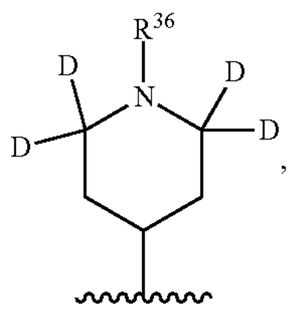
and R^{36} is selected from the group consisting of methyl, ethyl, isopropyl, isobutyl, —CH_2CH_2F, —CH_2CHF_2, —CH_2CF_3, —$CH_2CF_2CH_3$, —$CH_2C(CH_3)_2F$, —$CH_2CH_2CF_3$, —$(CH_2CH_2)OMe$, —$(CH_2CH_2)OiPr$,



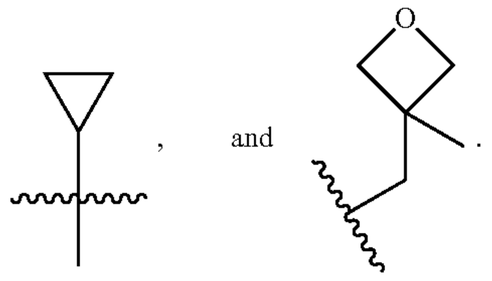
and

In some embodiments, R^6 is selected from the group consisting of:



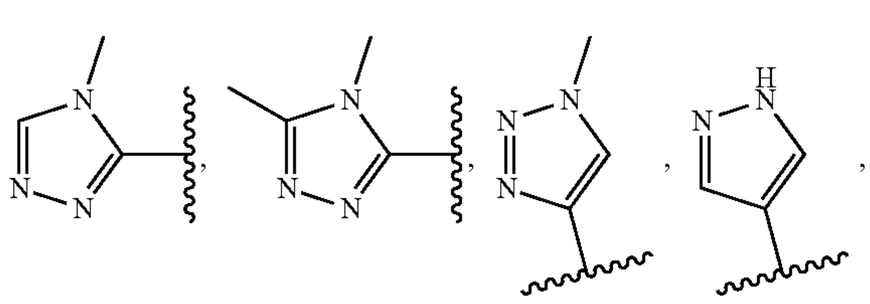


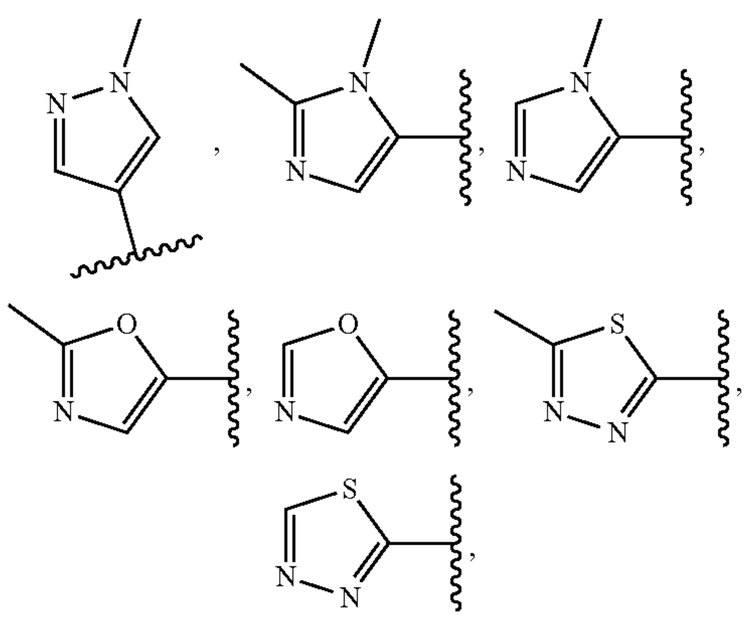
and R^{36} is selected from the group consisting of methyl, ethyl, isopropyl, isobutyl, —CH_2CH_2F, —CH_2CHF_2, —CH_2CF_3, —$CH_2CF_2CH_3$, —$CH_2C(CH_3)_2F$, —$CH_2CH_2CF_3$, —$(CH_2CH_2)OMe$, —$(CH_2CH_2)OiPr$,



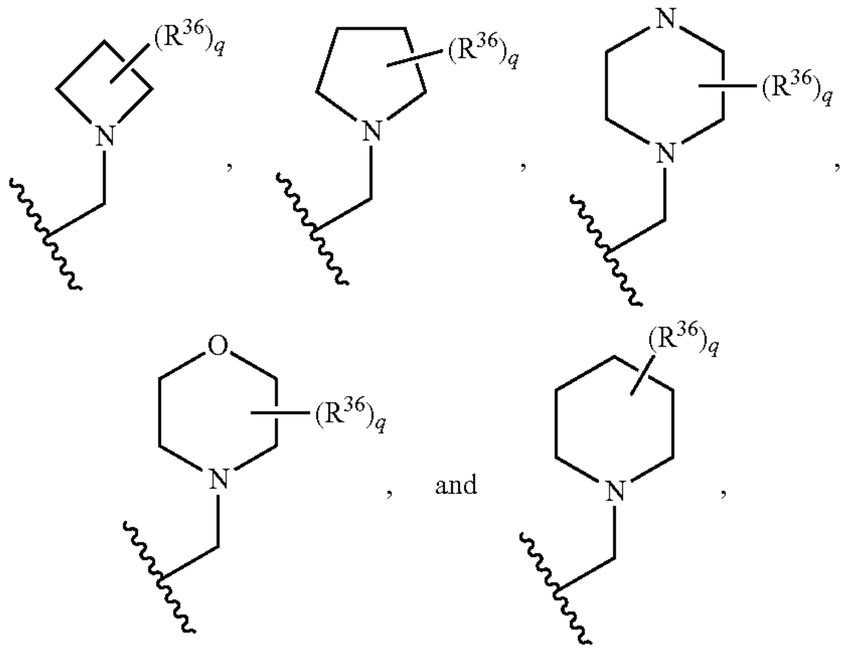
and

In some embodiments, R^3 is selected from the group consisting of:



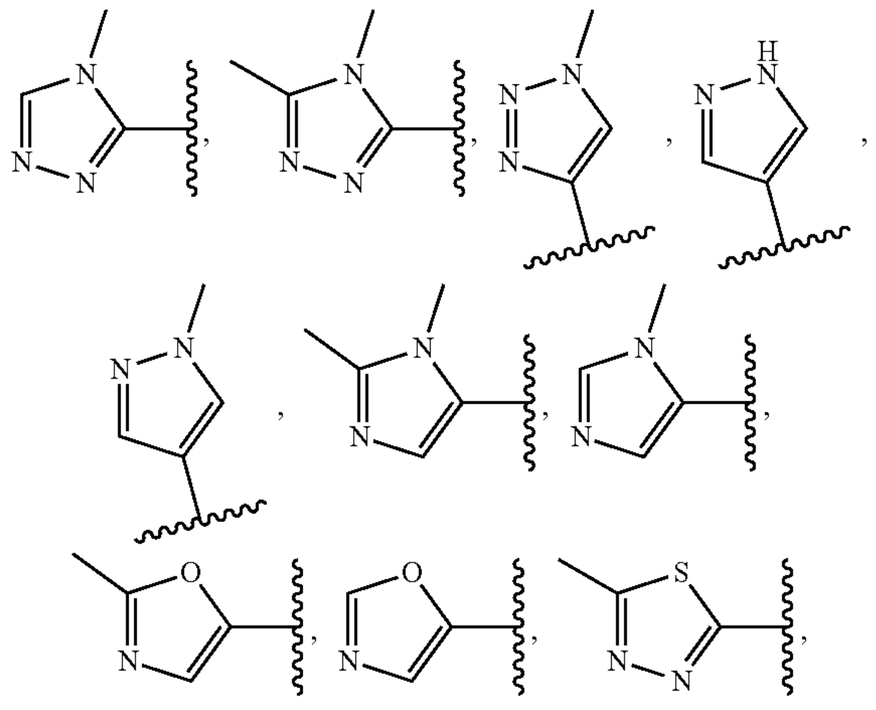


R^6 is selected from the group consisting of:



q is 0 to 2, and each R^{36} is independently selected from the group consisting of F, methyl, and —CF_3.

In some embodiments, R^3 is selected from the group consisting of:



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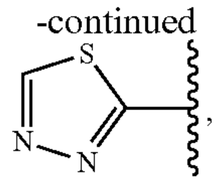
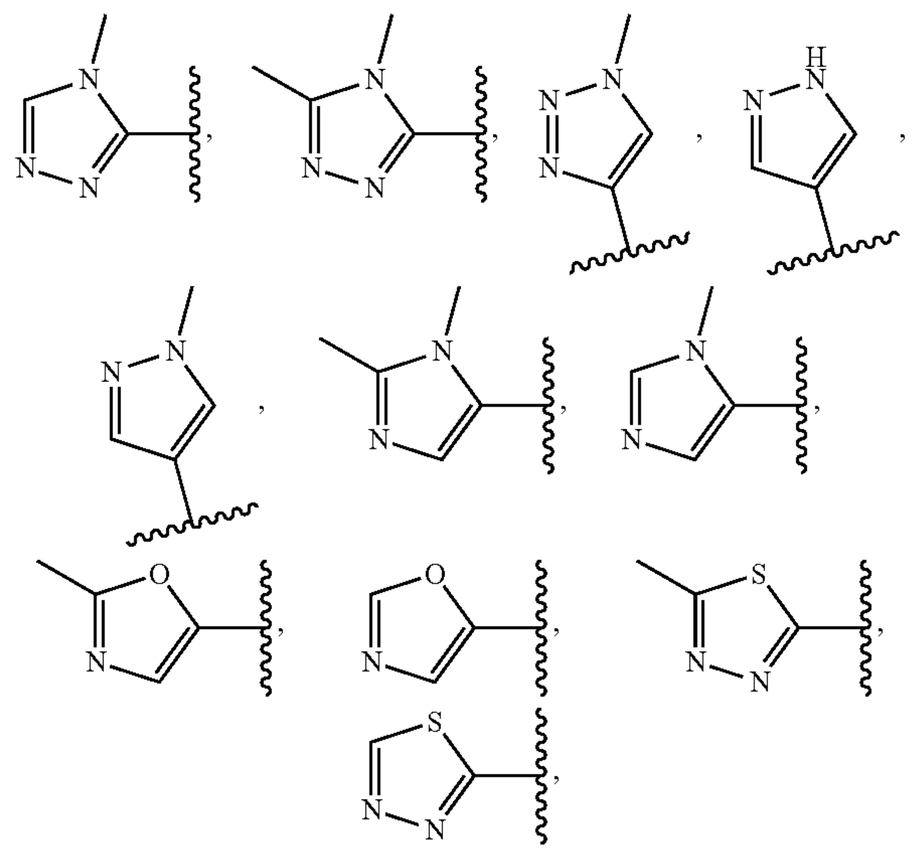


and R^6 is selected from the group consisting of -cyclopropyl, -cyclobutyl, -cyclopentyl, -cyclohexyl each optionally substituted with 1-2 R^{37} and —(CH_2)cyclopropyl, —(CH_2)cyclobutyl, —(CH_2)cyclopentyl, and —(CH_2)cyclohexyl, each optionally substituted with 1-2 R^{37}, and each R^{37} is independently selected from the group consisting of F, methyl, —CF_3, —OCF_3, and —OMe.

In some embodiments, R^3 is selected from the group consisting of:



and R^6 is —$CF(C_{1\text{-}3}\ alkyl)_2$; wherein the alkyl of —$CF(C_{1\text{-}3}\ alkyl)_2$ is optionally substituted with 1-2 fluorines.

Illustrative compounds of Formula (I) are shown in Table 1.

TABLE 1

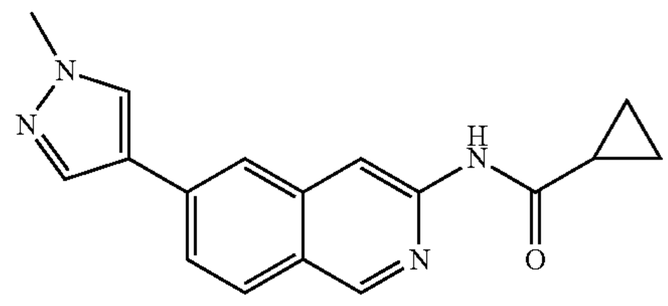
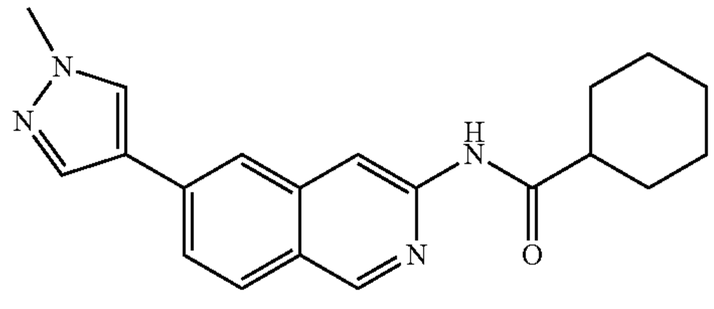
1	
2	

TABLE 1-continued

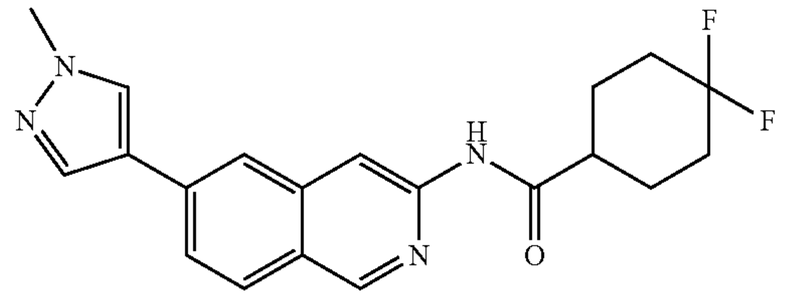
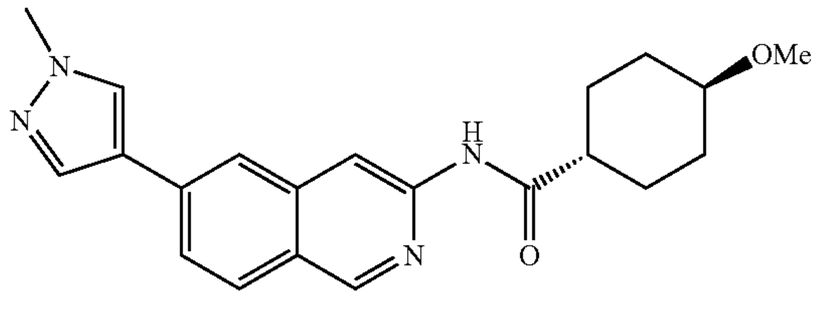
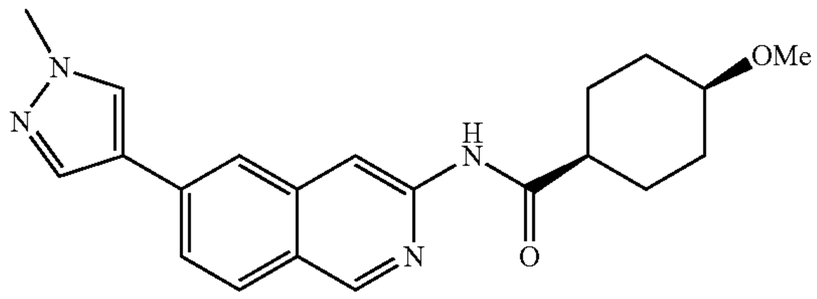
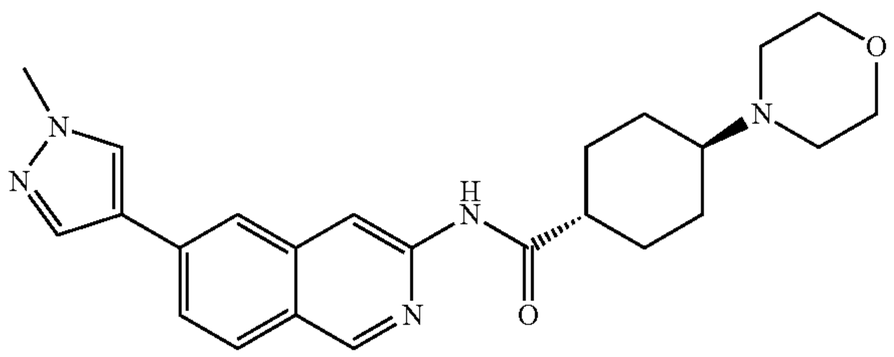
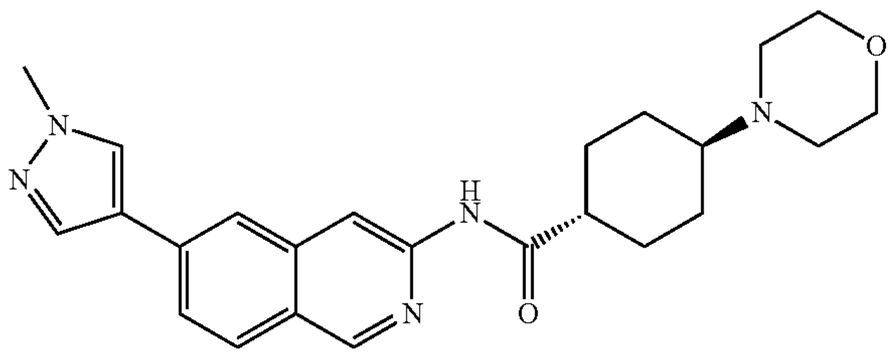
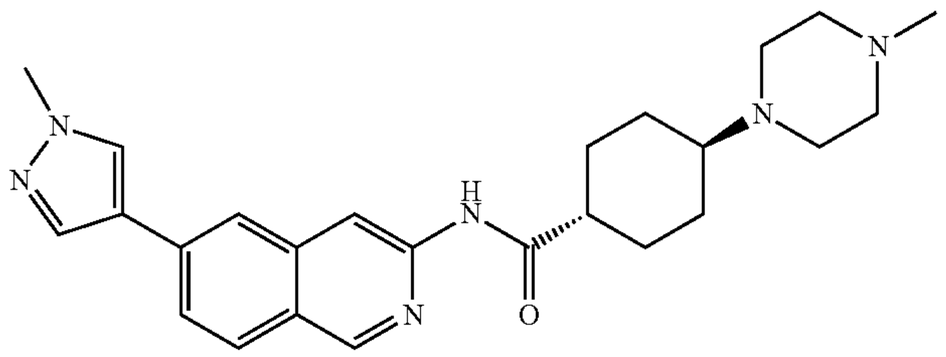
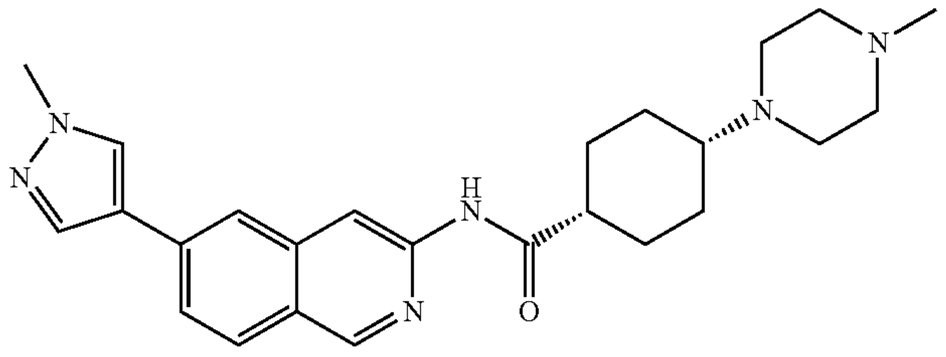
	3
	4
	5
	6
	7
	8
	9

TABLE 1-continued

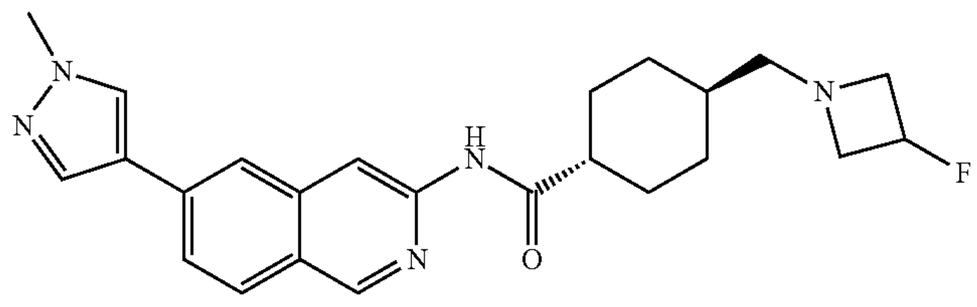
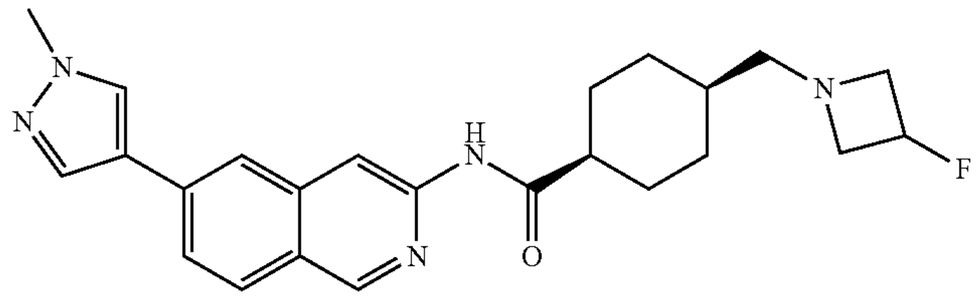
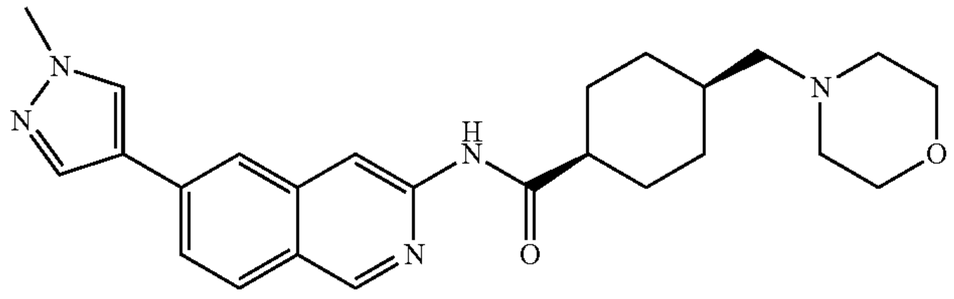
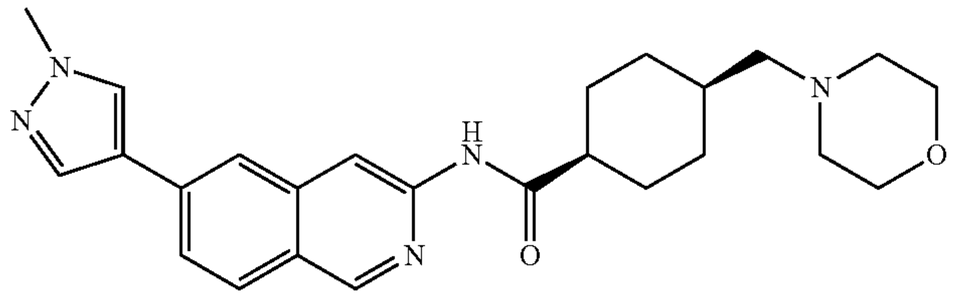
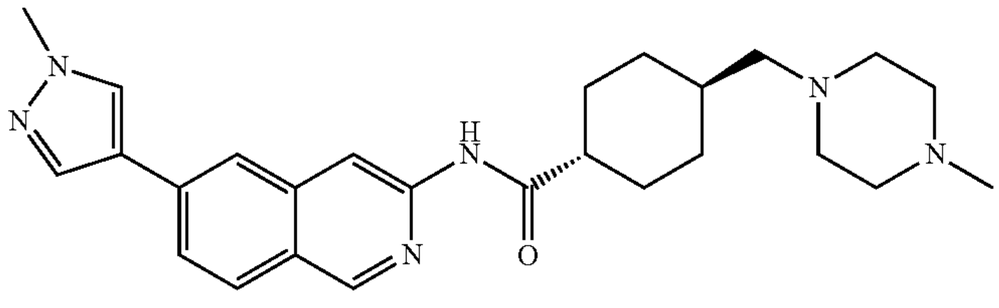
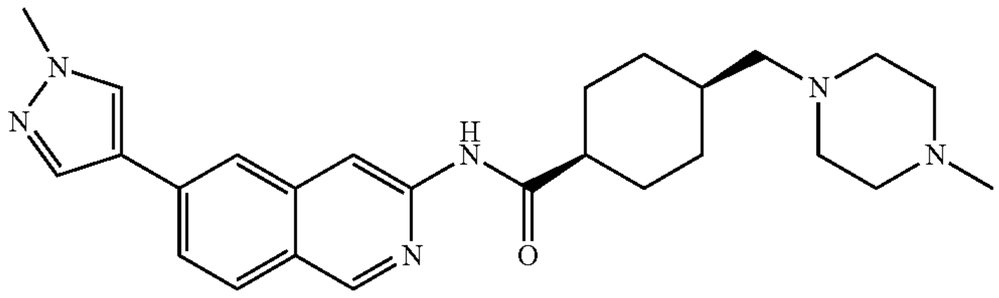
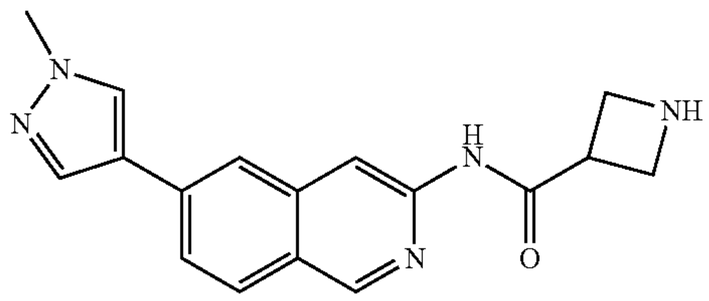
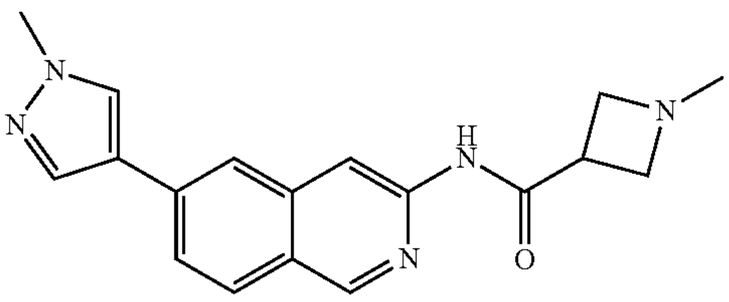
10	
11	
12	
13	
14	
15	
16	
17	

TABLE 1-continued

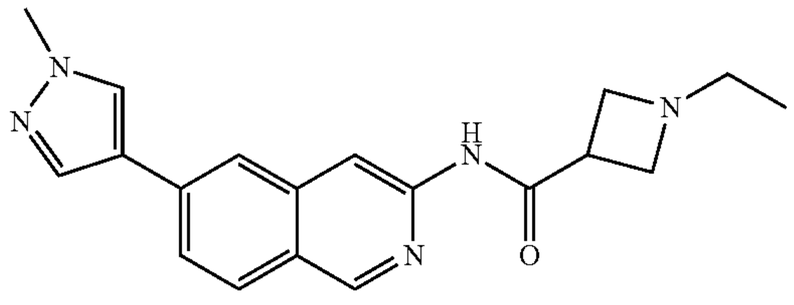
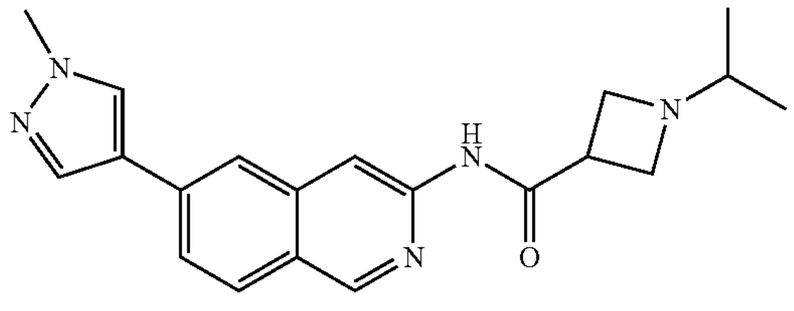
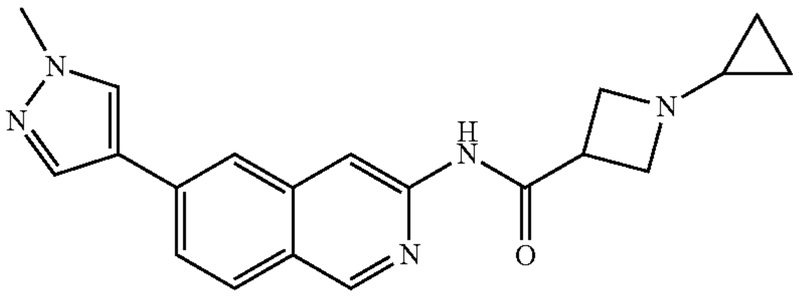
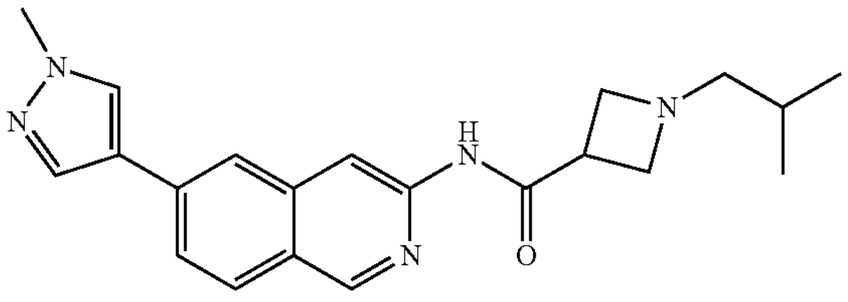
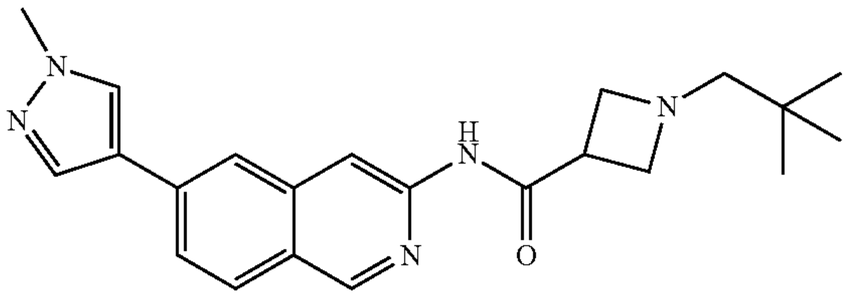
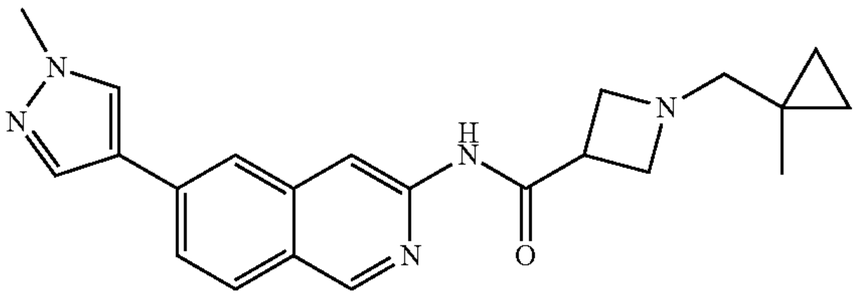
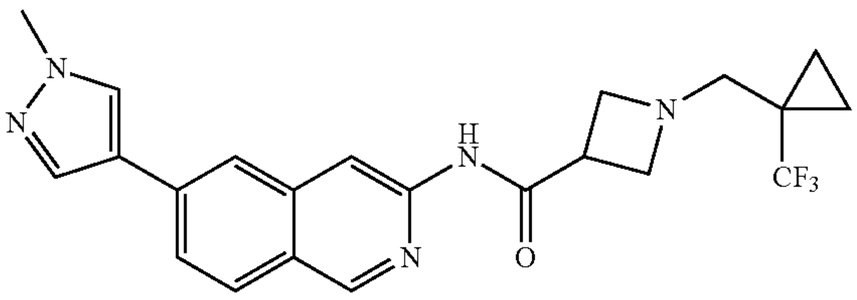
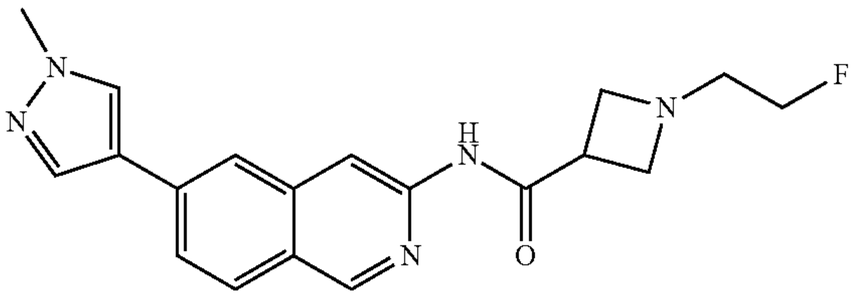
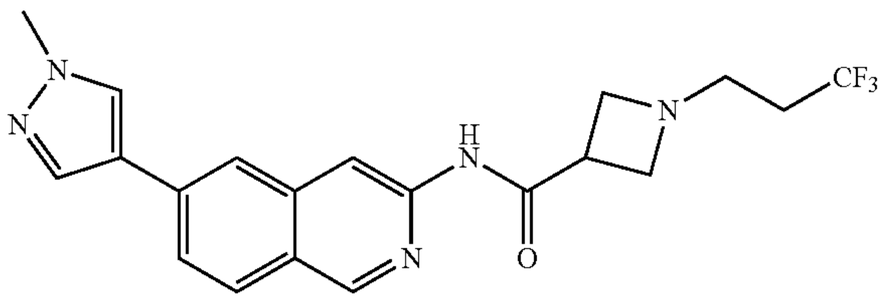
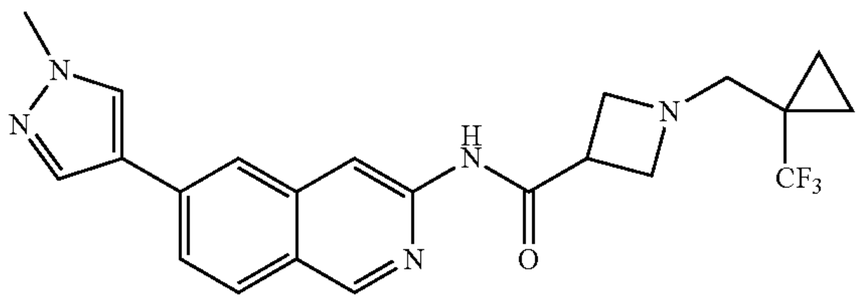
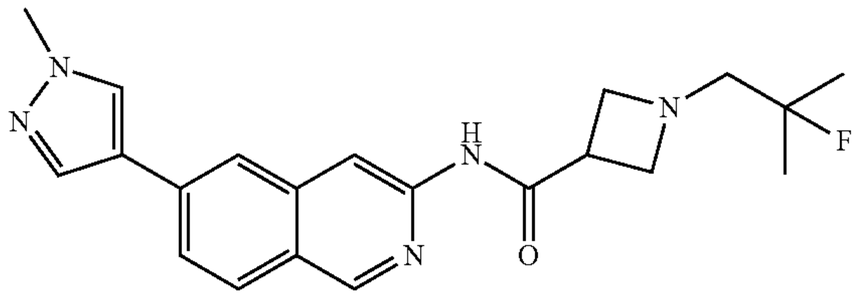
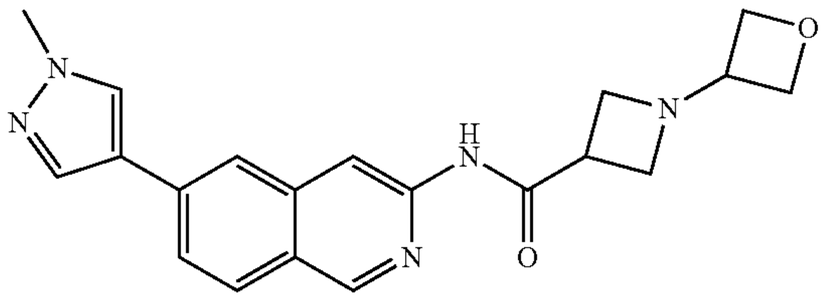
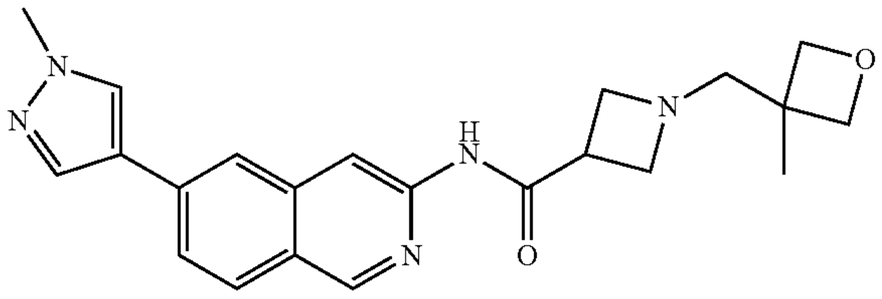
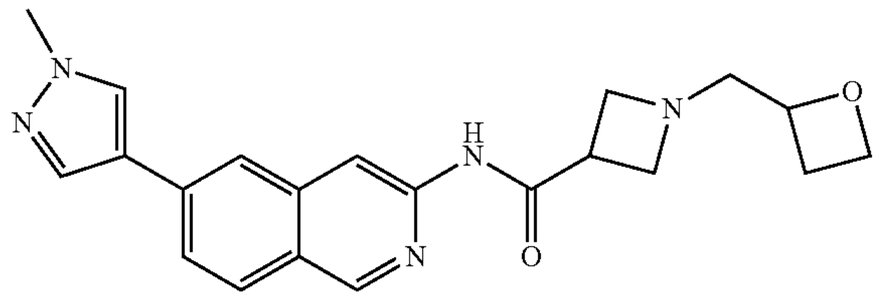
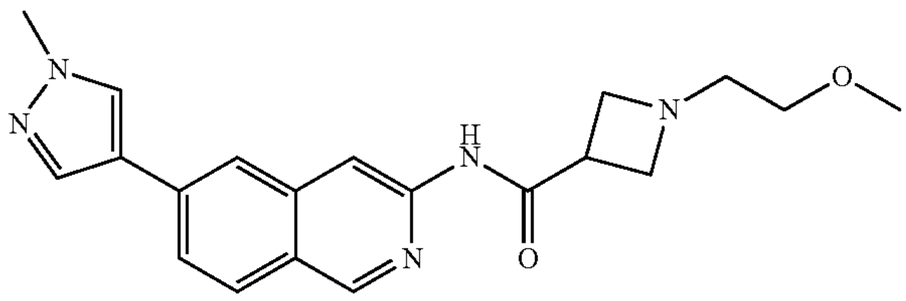
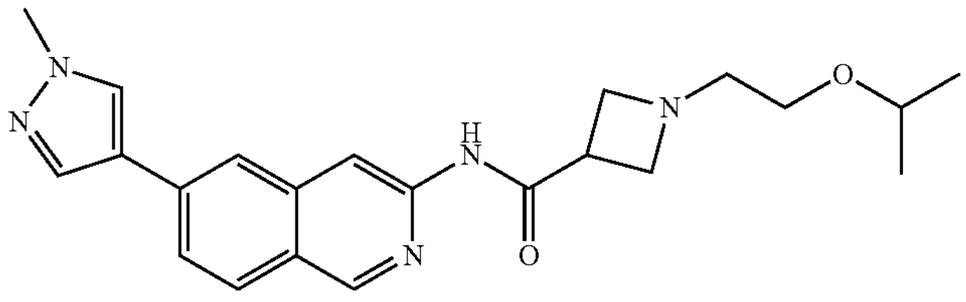
18	
19	
20	
21	
22	
23	
24	
25	

TABLE 1-continued

26	
27	
28	
29	
30	
31	
32	
33	

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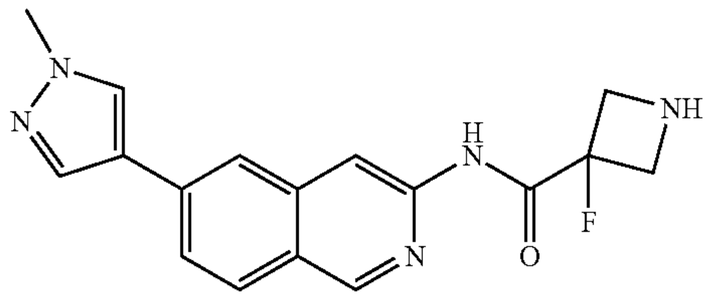
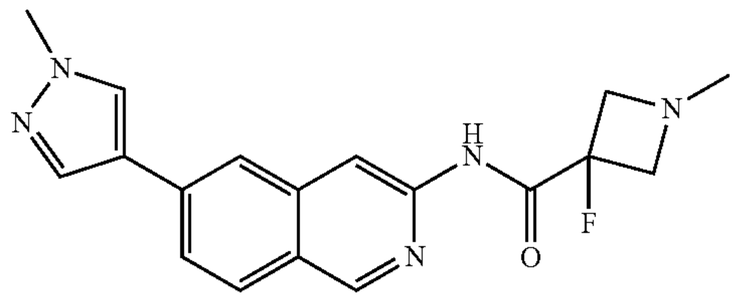
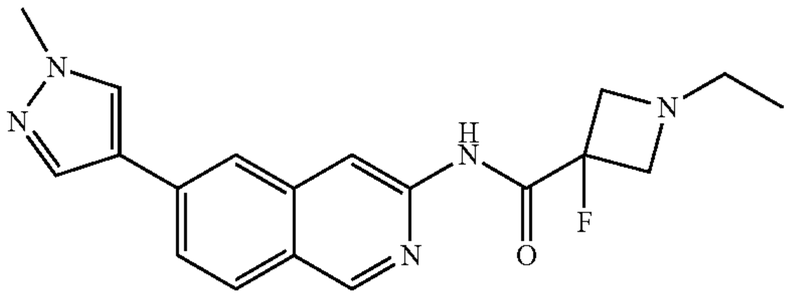
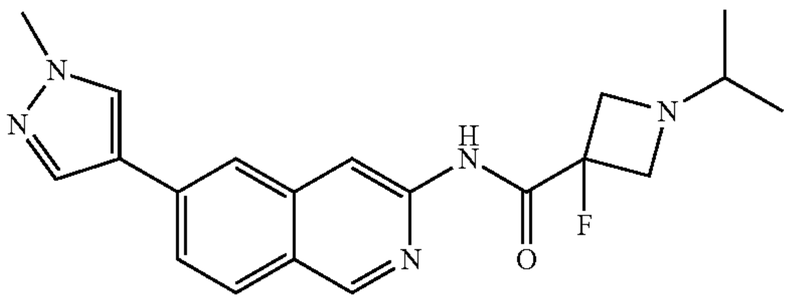
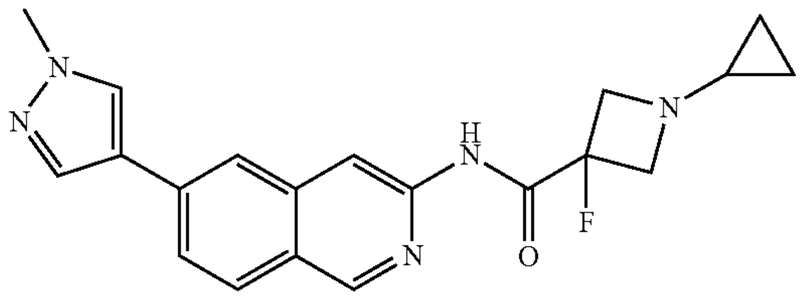
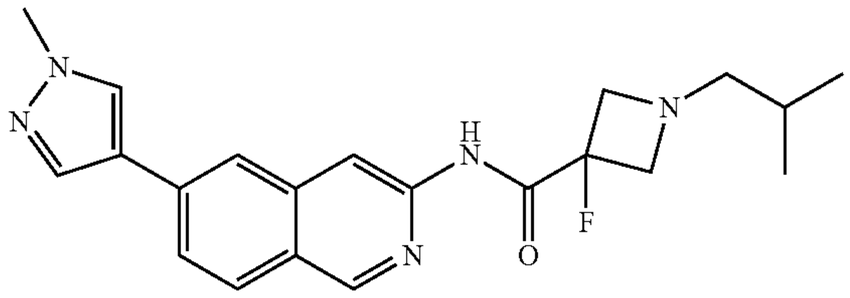
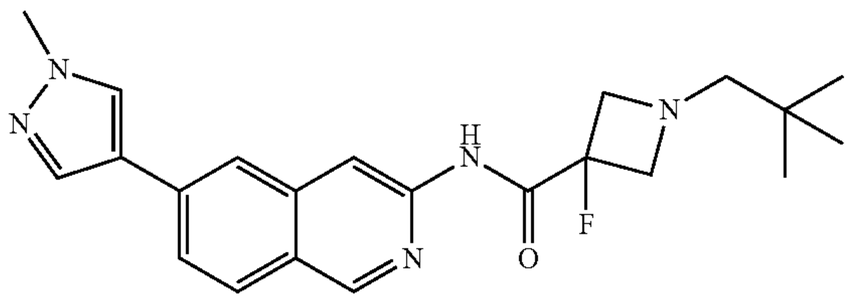
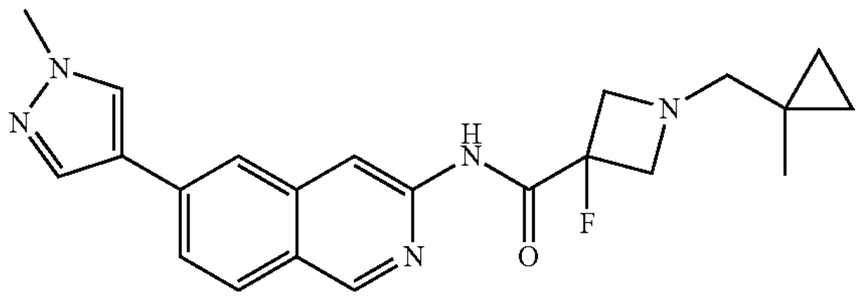
34	
35	
36	
37	
38	
39	
40	
41	

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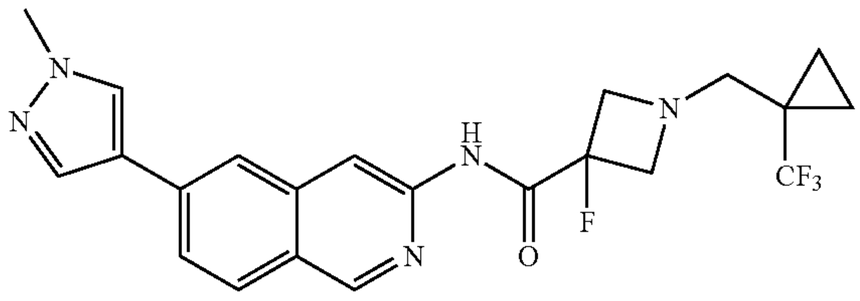
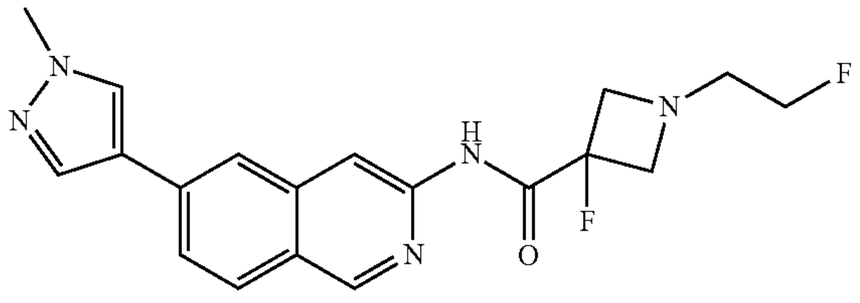
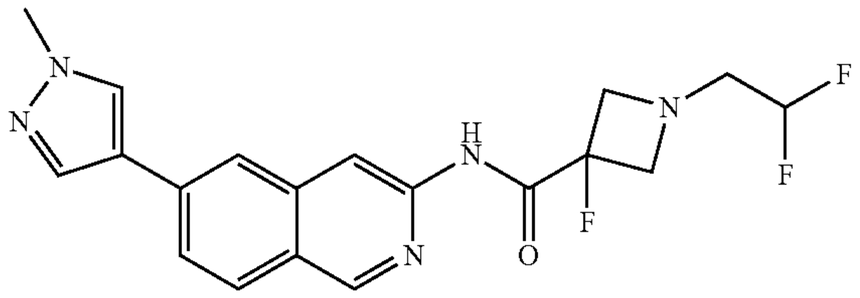
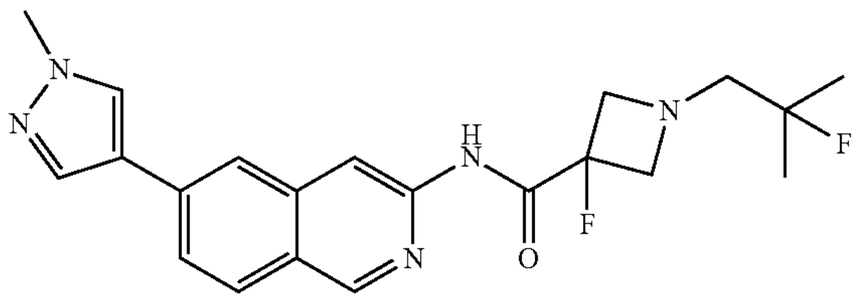
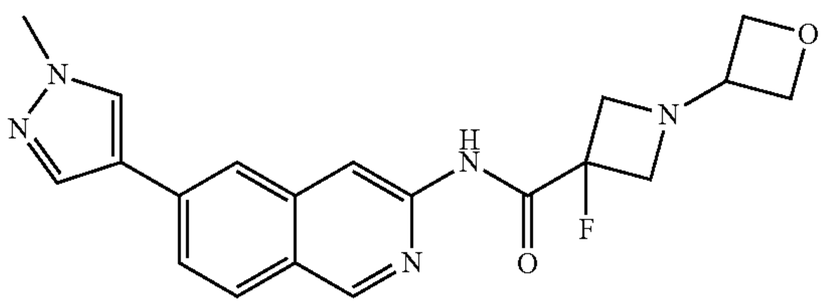
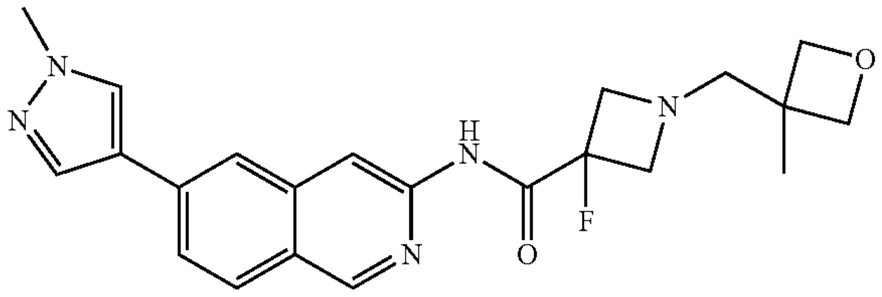
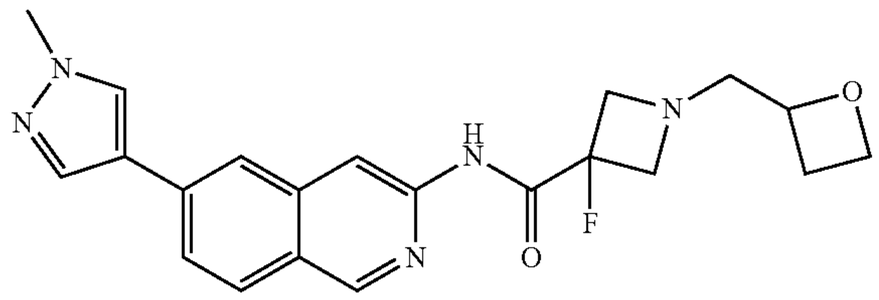
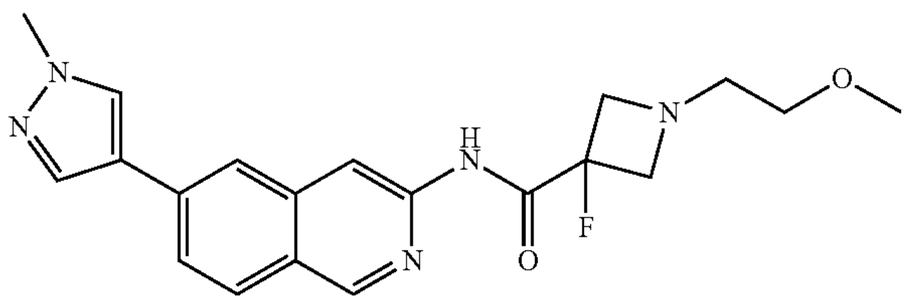
42	
43	
44	
45	
46	
47	
48	
49	

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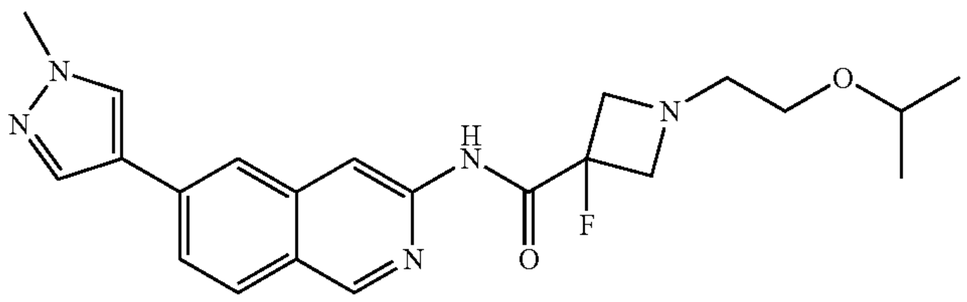
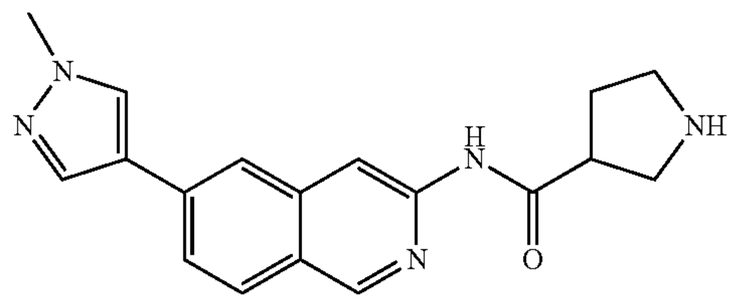
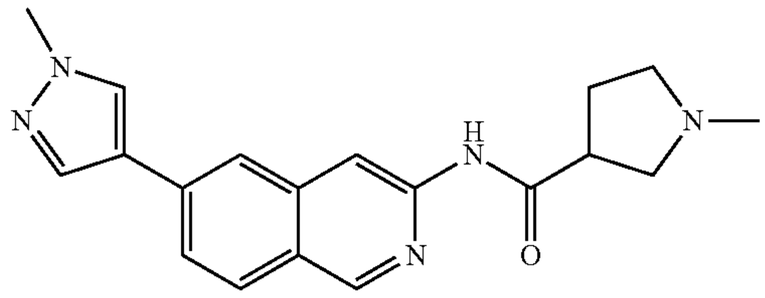
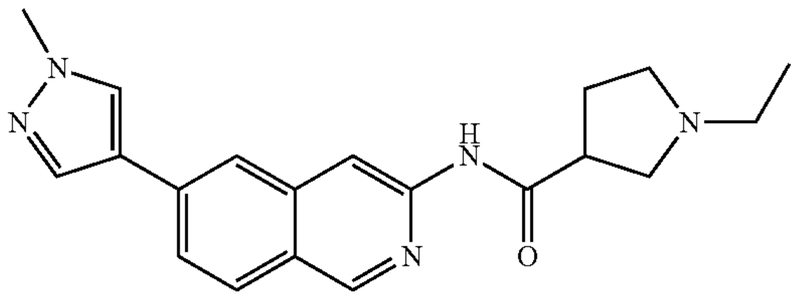
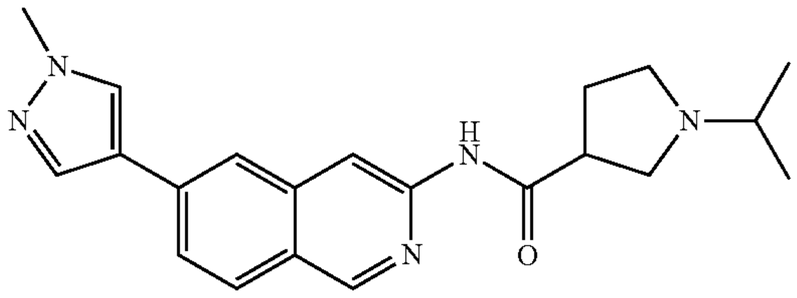
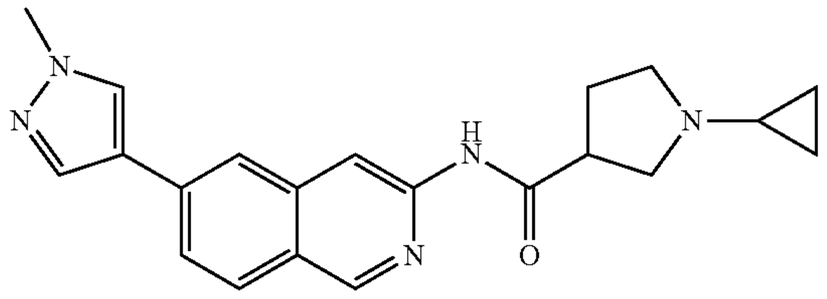
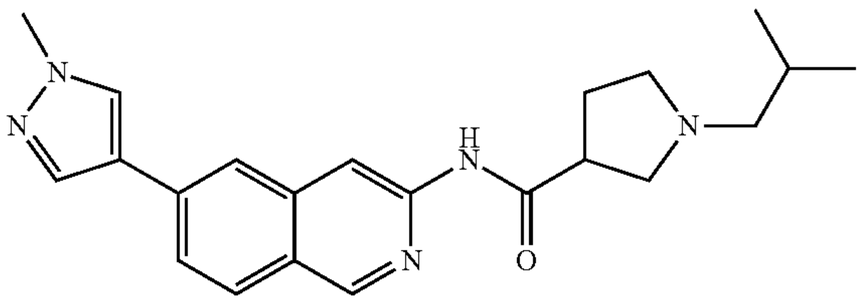
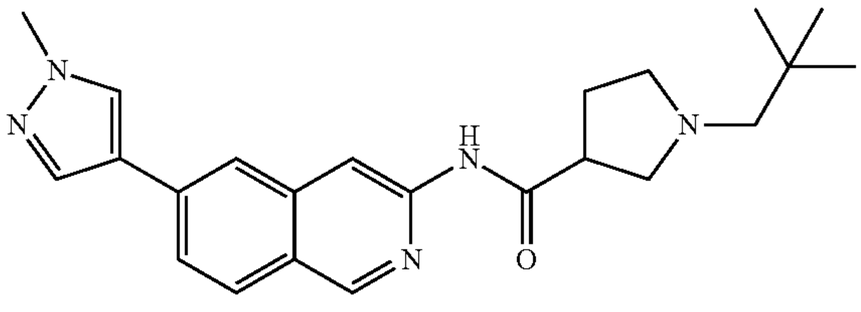
50	
51	
52	
53	
54	
55	
56	
57	

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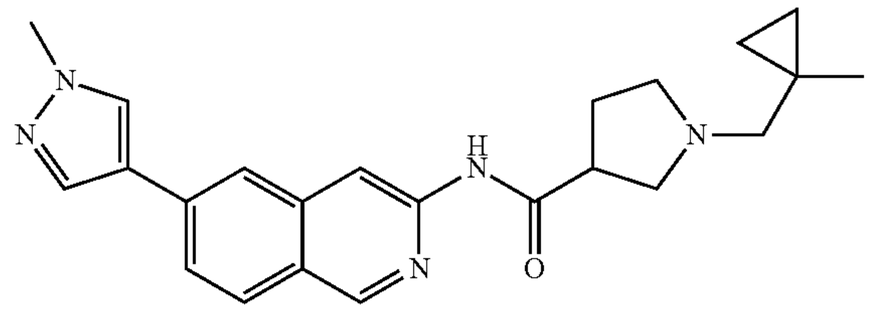
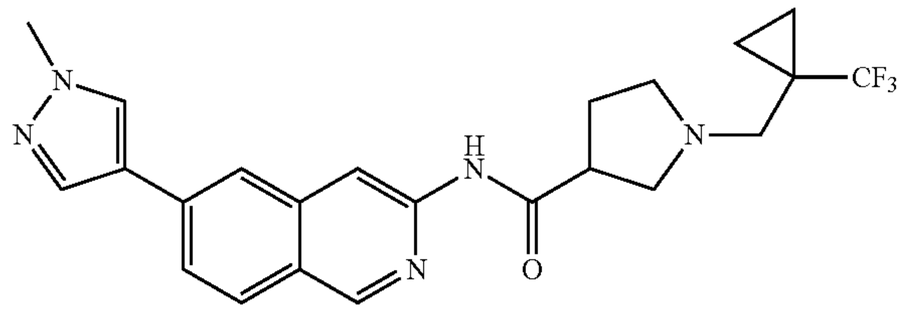
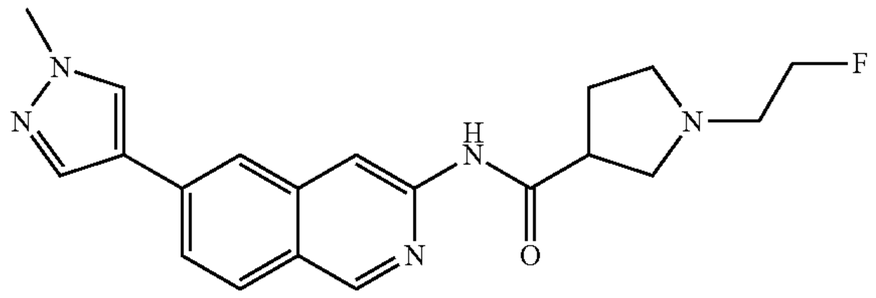
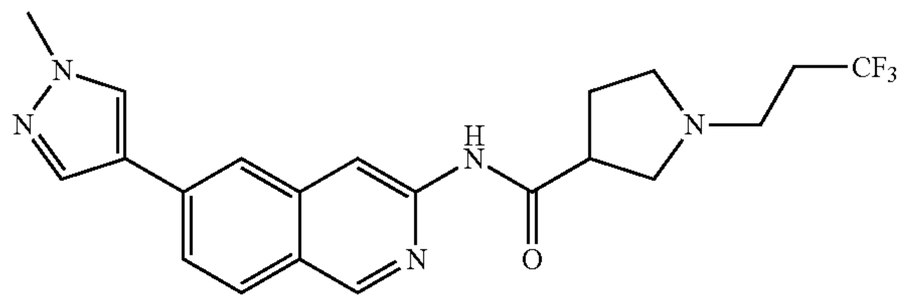
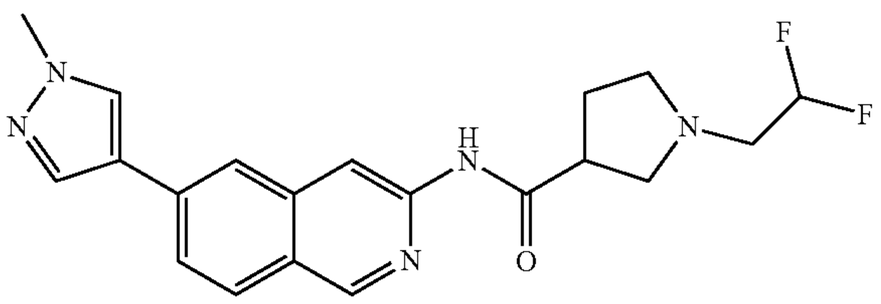
58	
59	
60	
61	
62	
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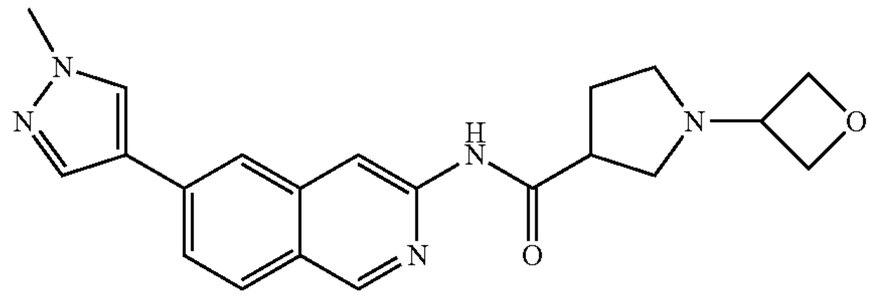
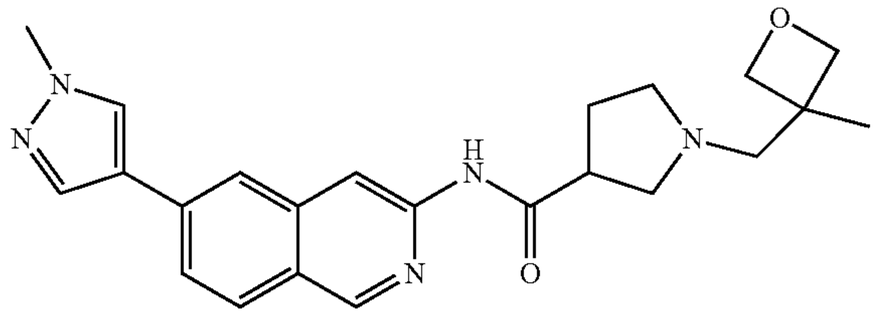
64	
65	

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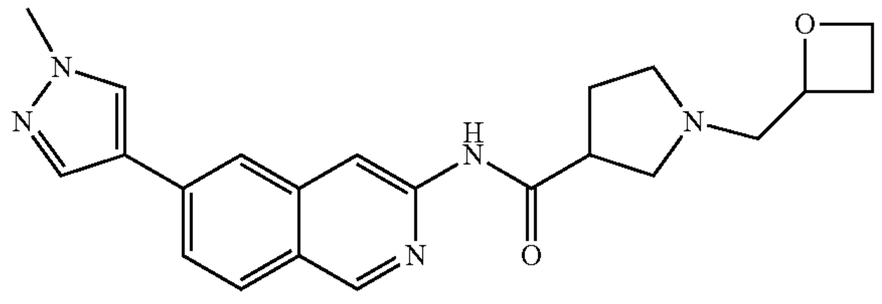

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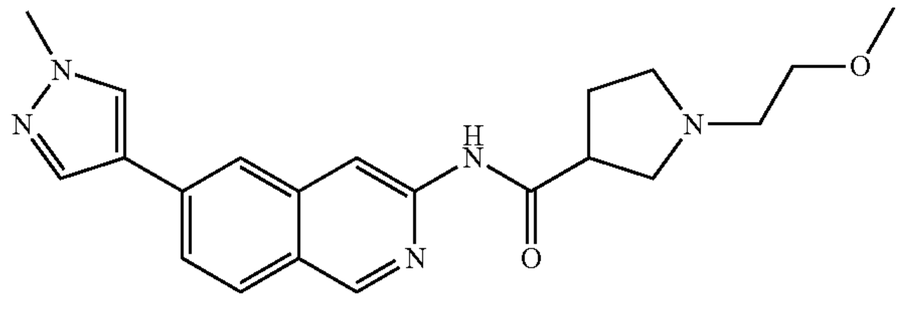

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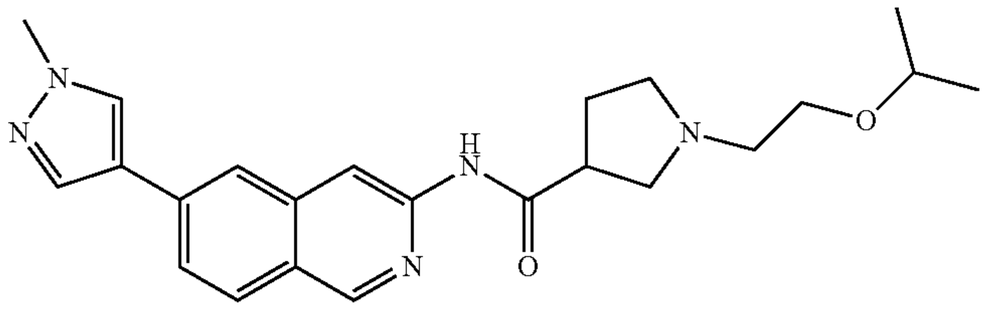

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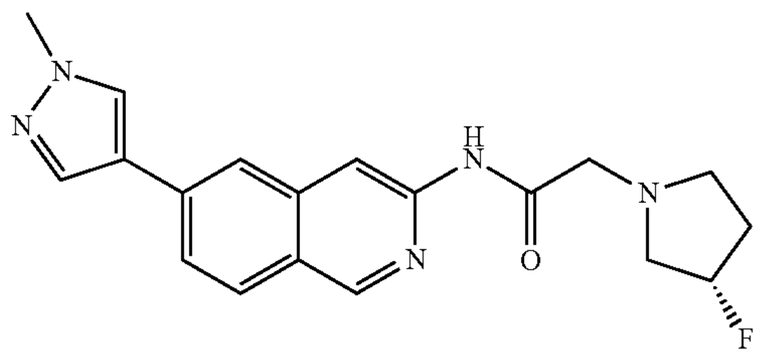

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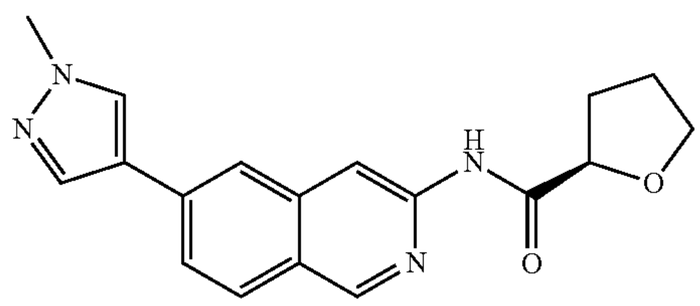

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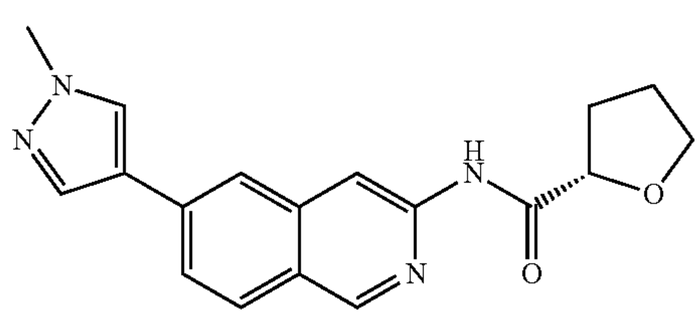

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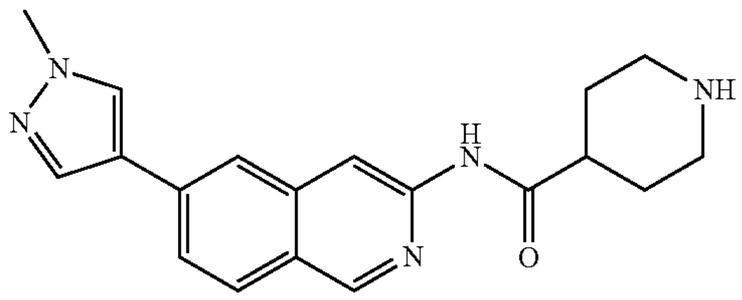

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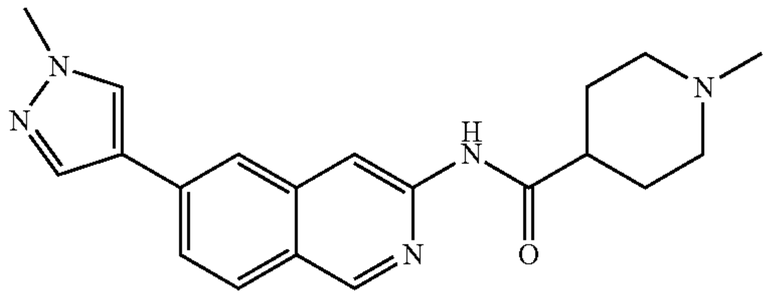

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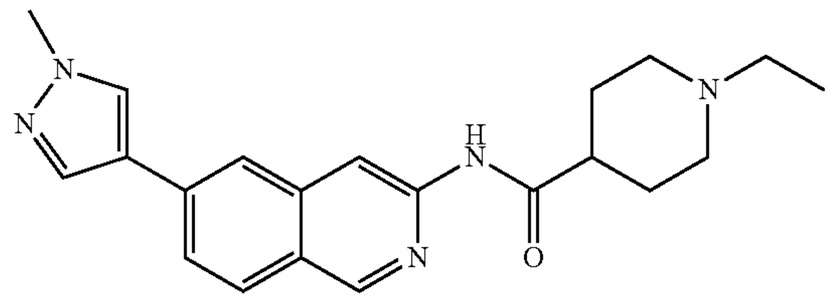
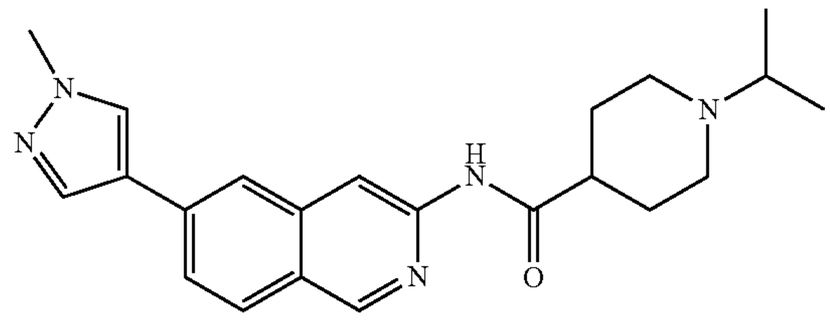
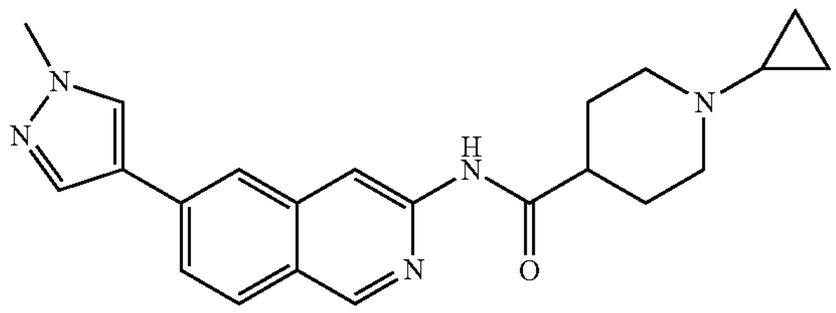
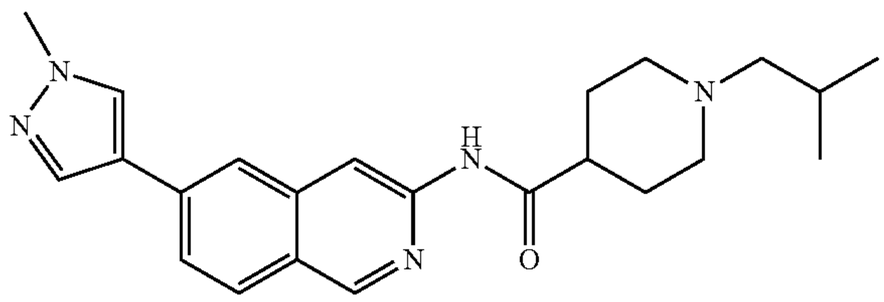
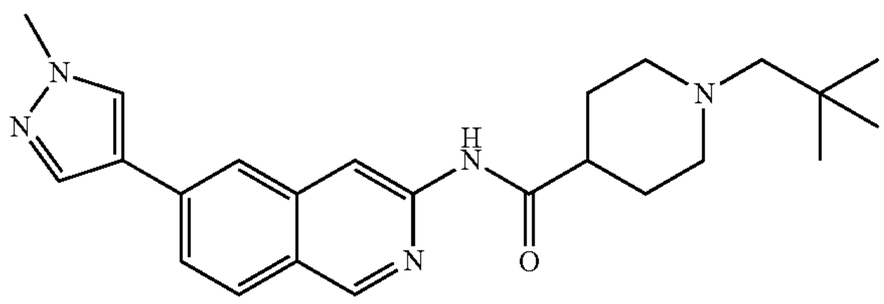
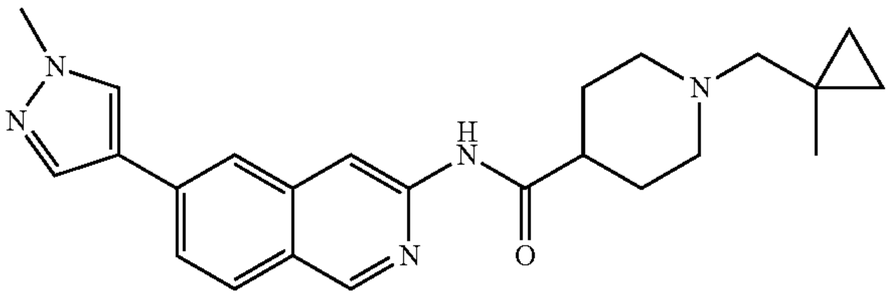
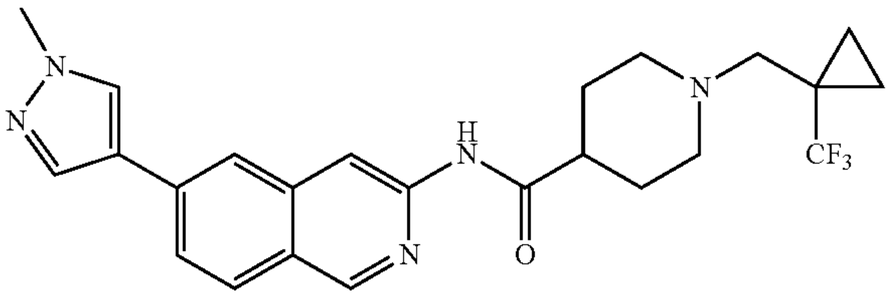
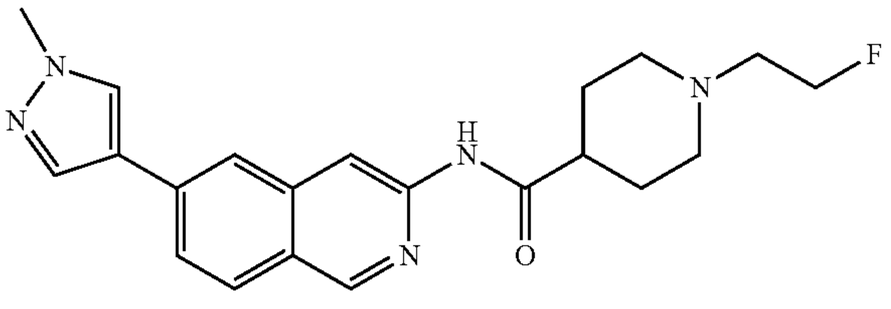
74	
75	
76	
77	
78	
79	
80	
81	

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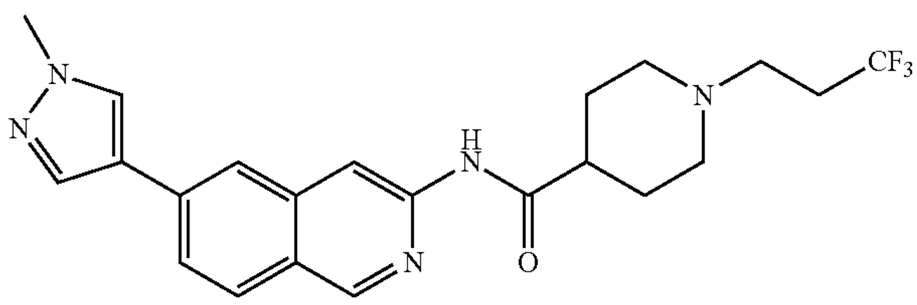
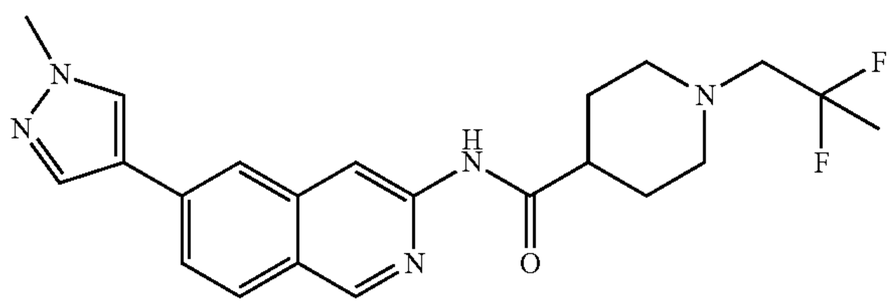
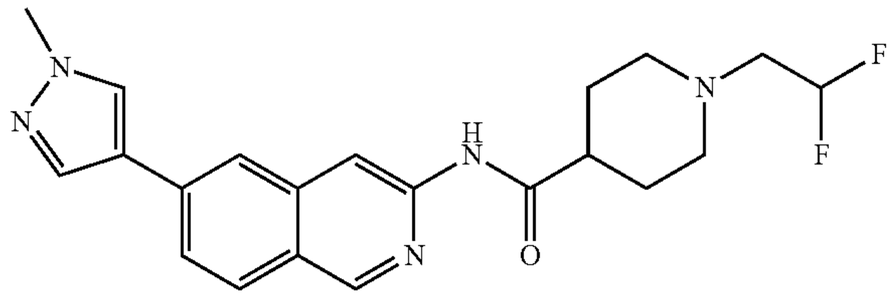
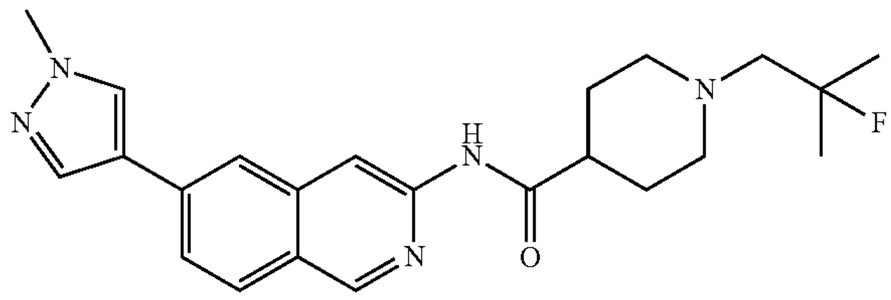
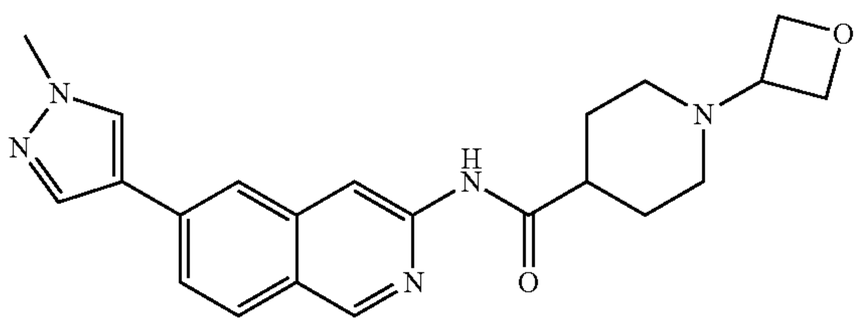
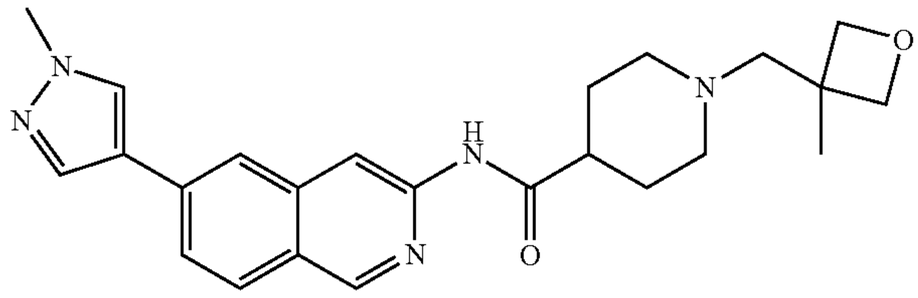
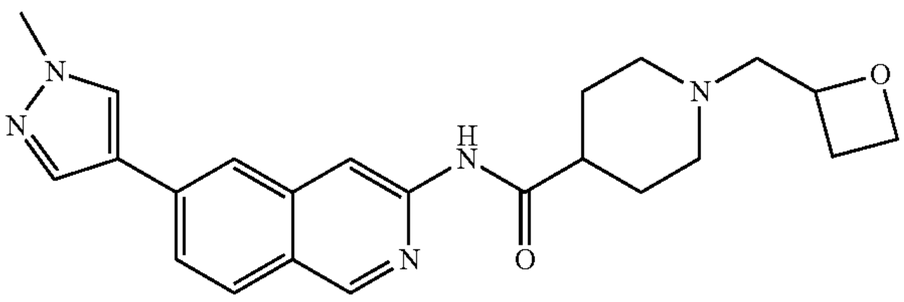
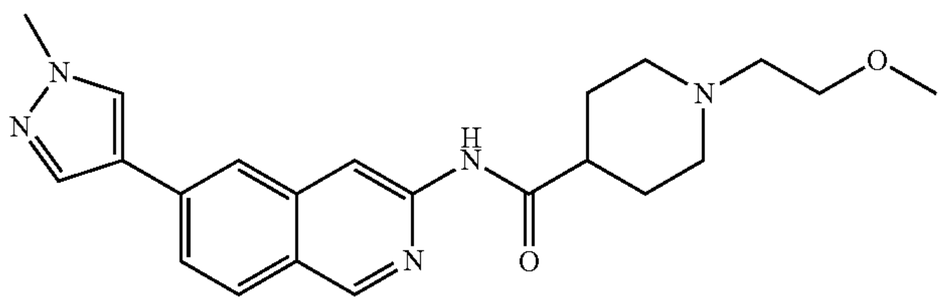
82	
83	
84	
85	
86	
87	
88	
89	

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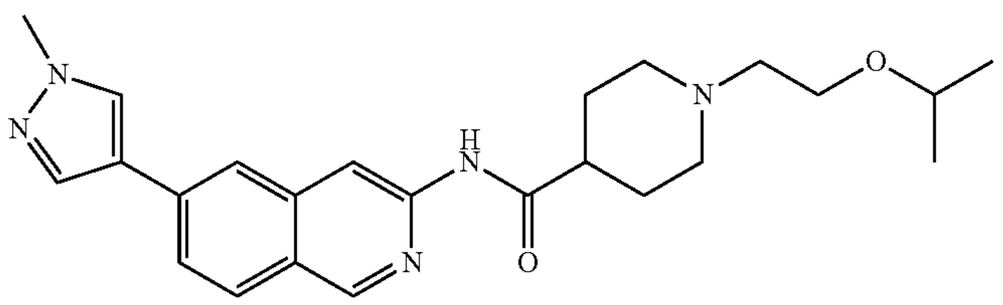
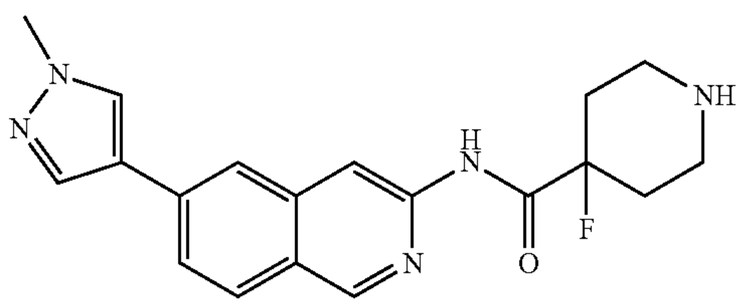
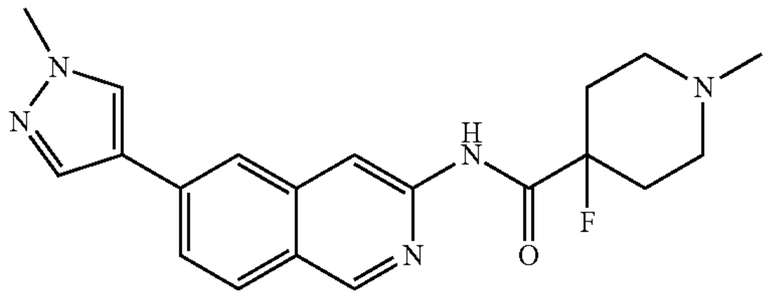
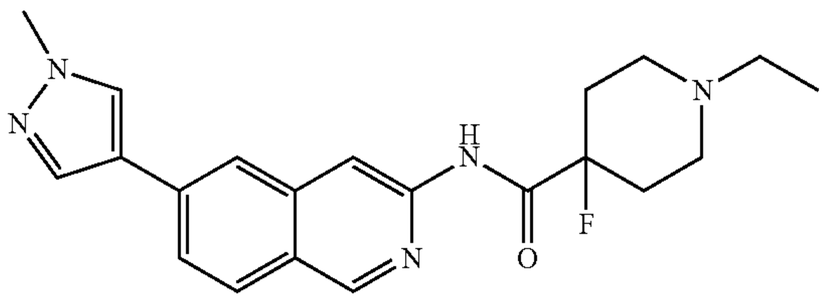
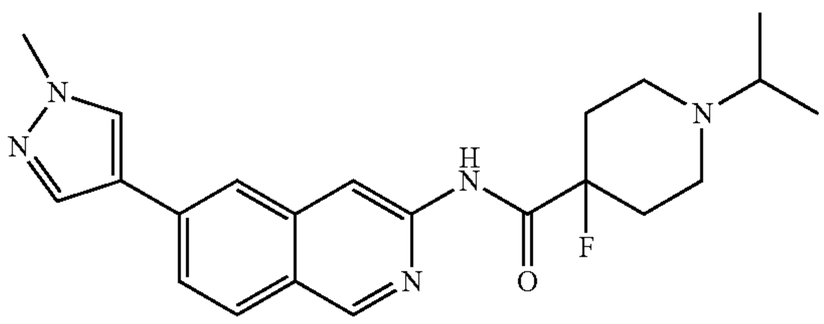
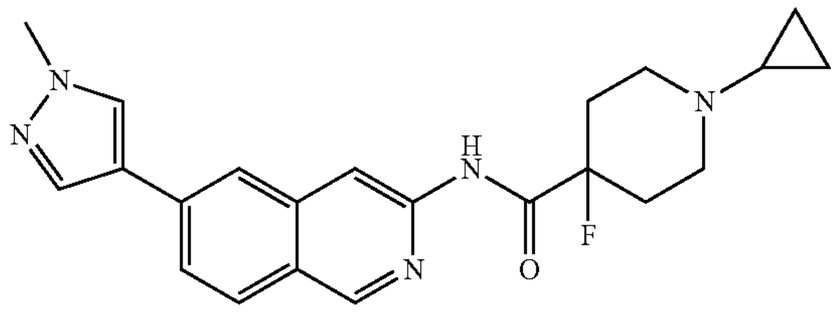
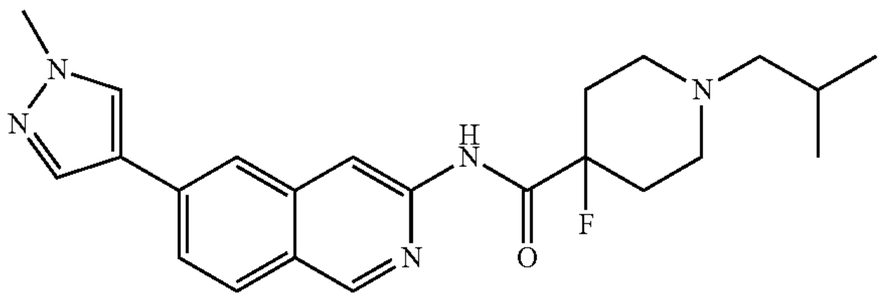
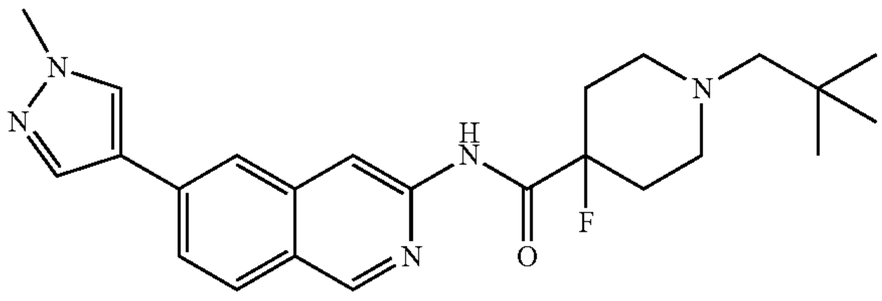
90	
91	
92	
93	
94	
95	
96	
97	

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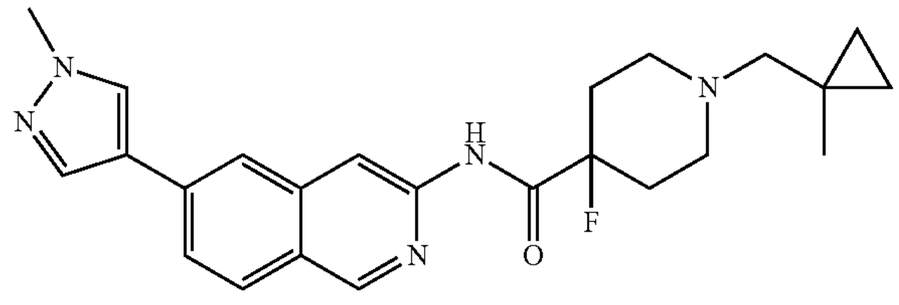

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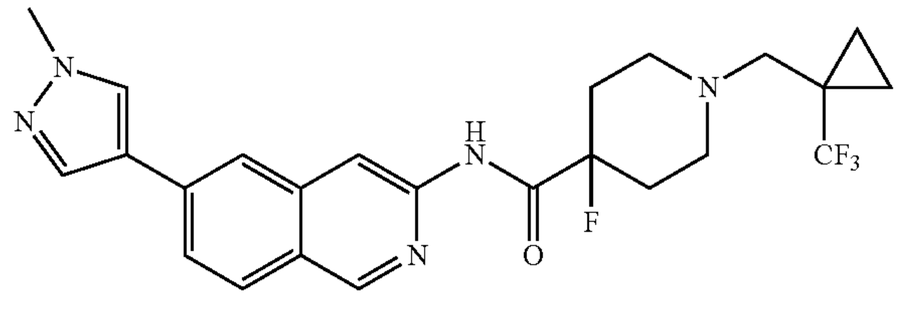

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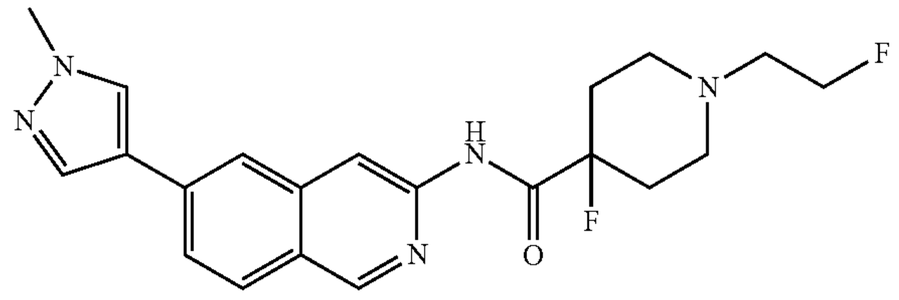

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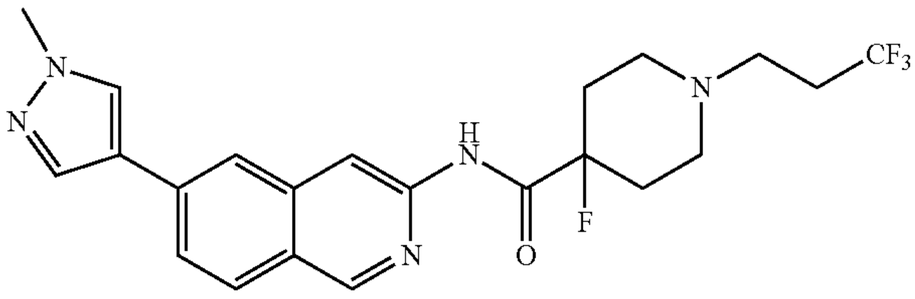

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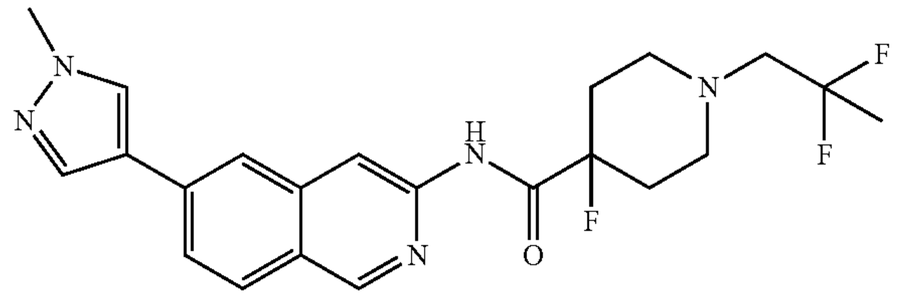

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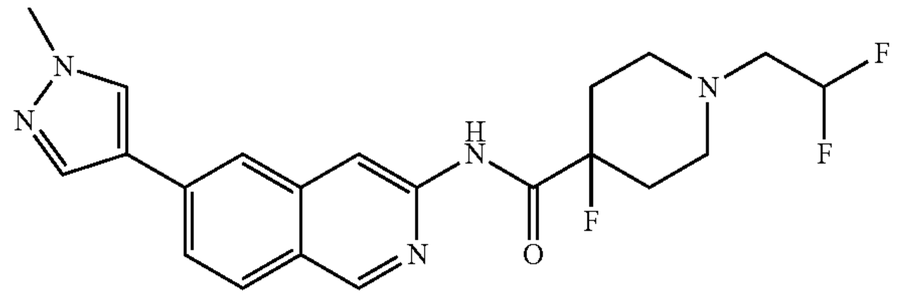

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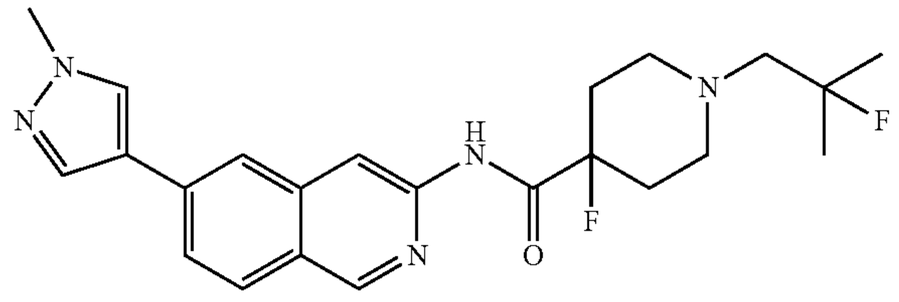

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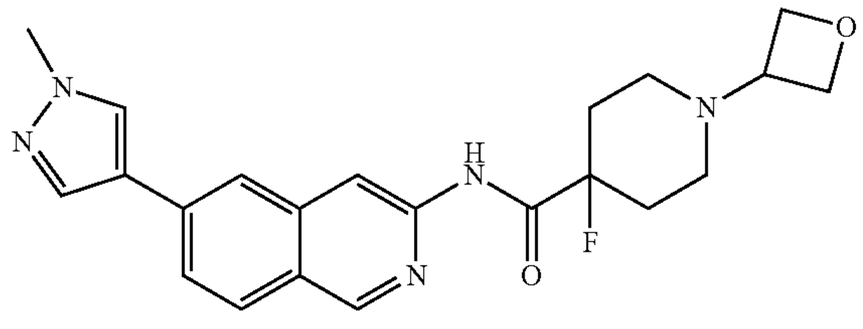

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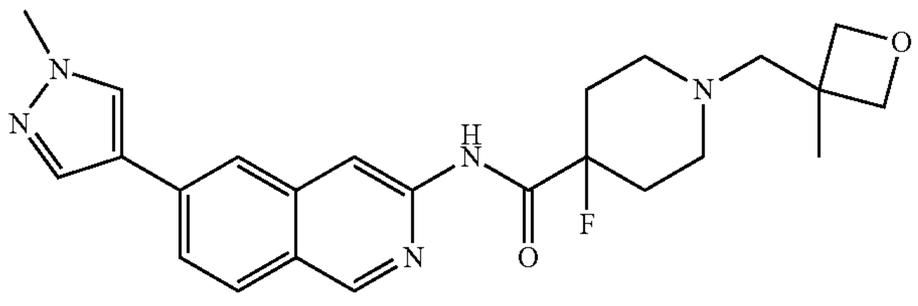

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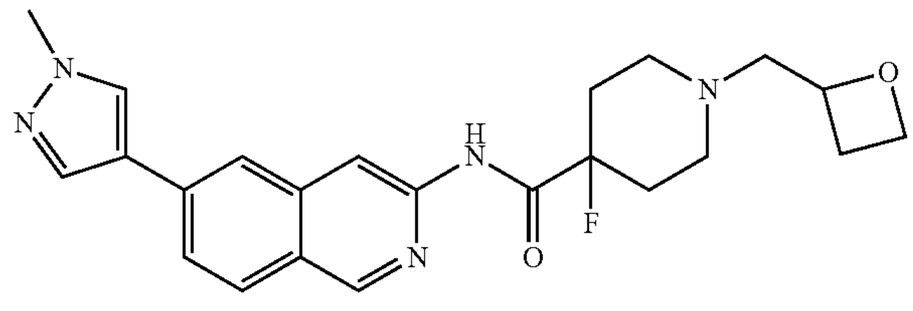

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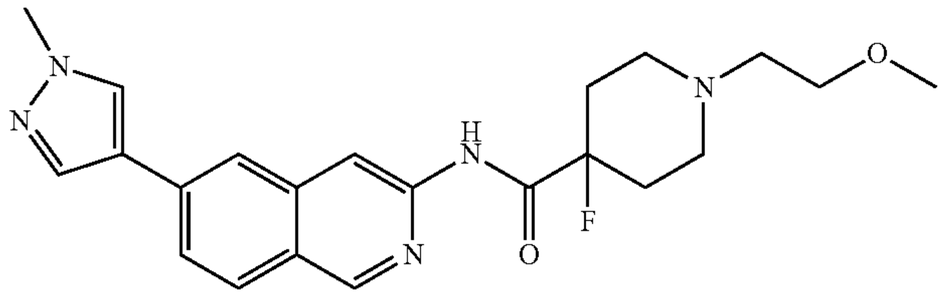

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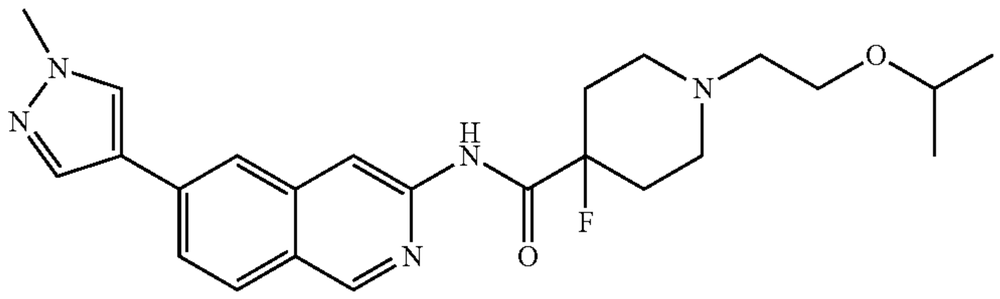

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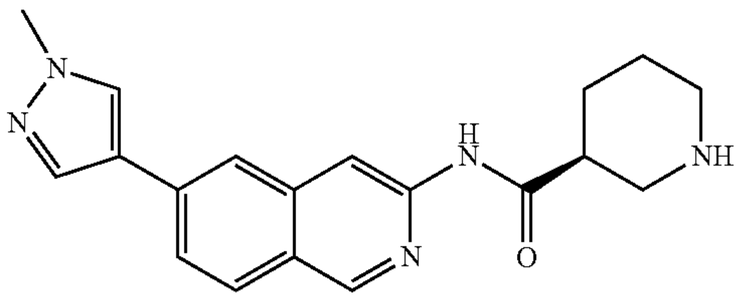

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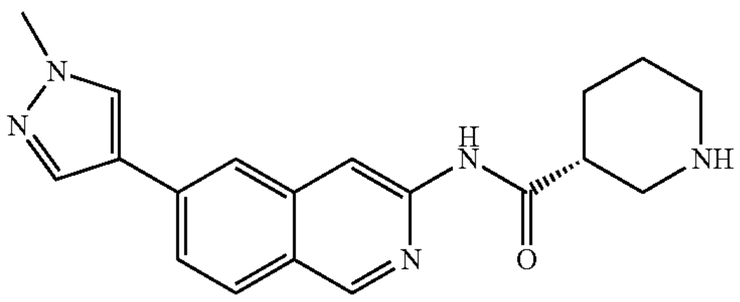

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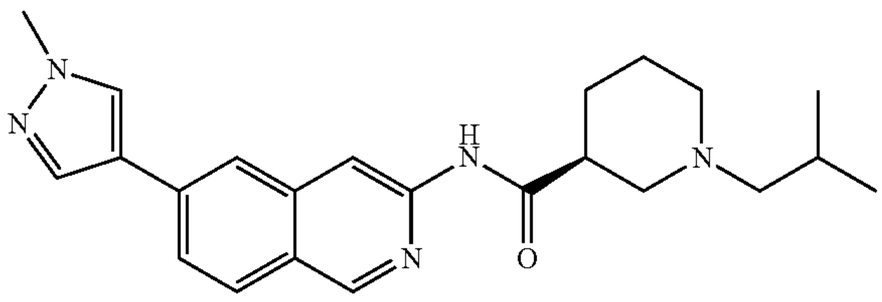

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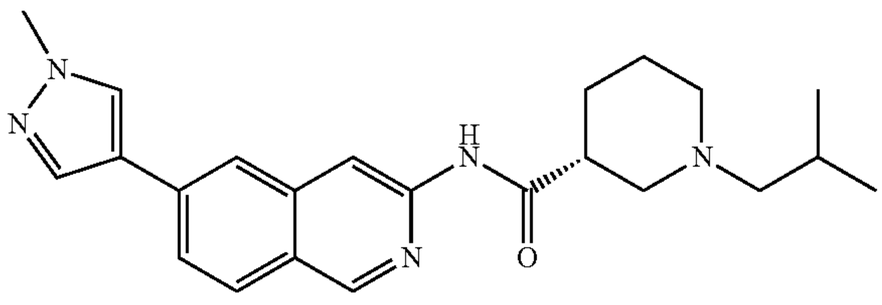

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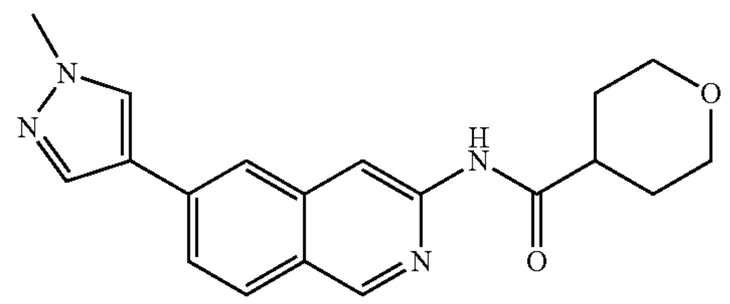
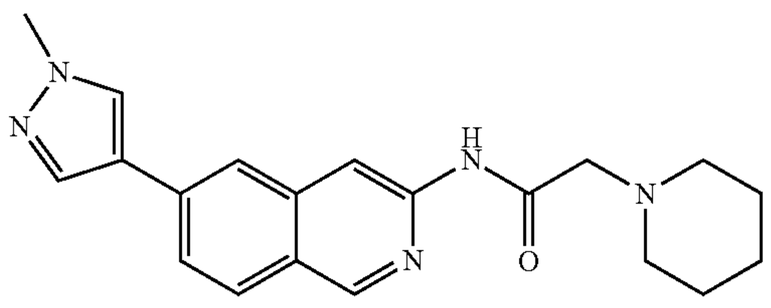
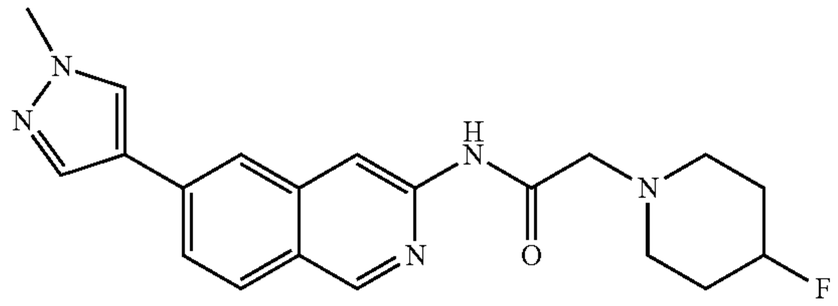
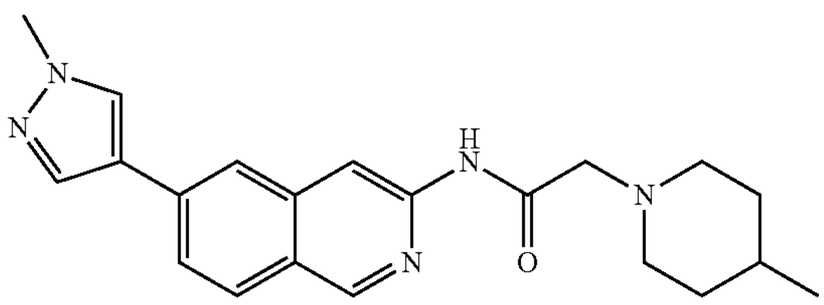
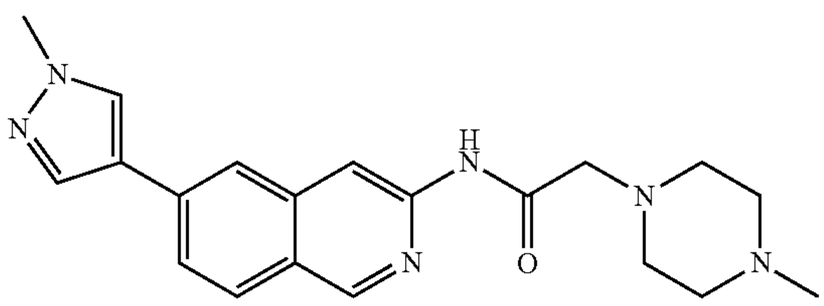
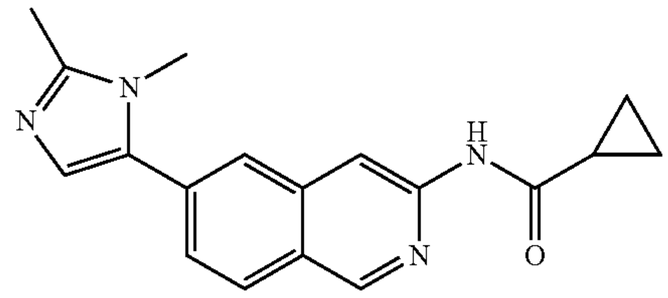
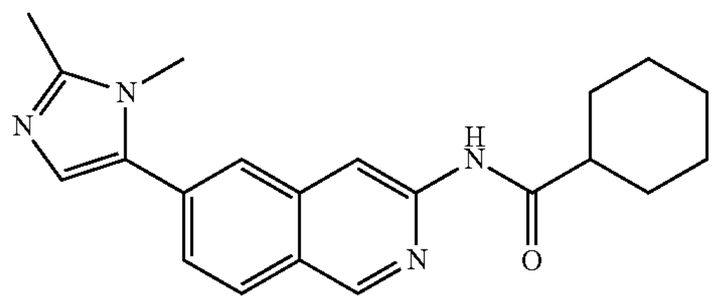
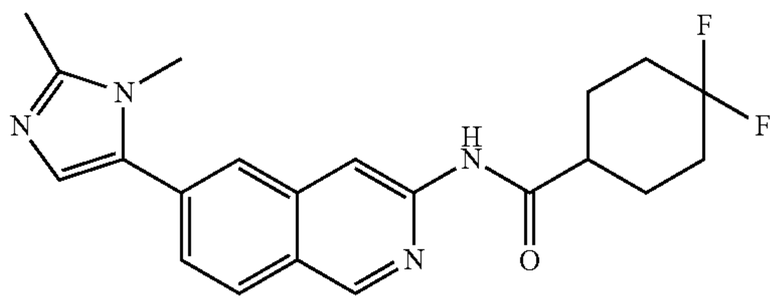
114	
115	
116	
117	
118	
119	
120	
121	

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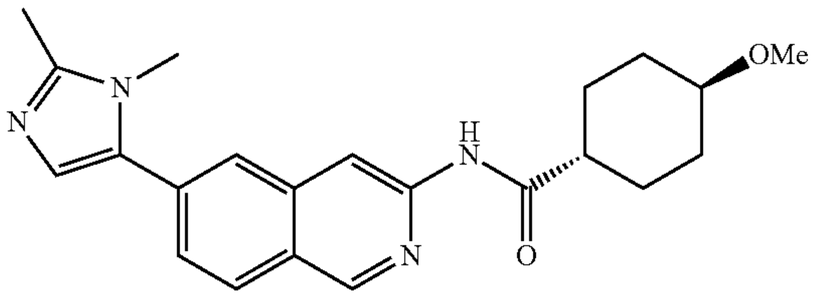
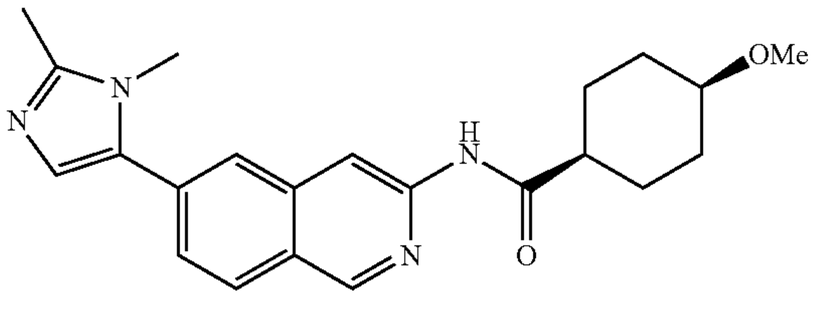
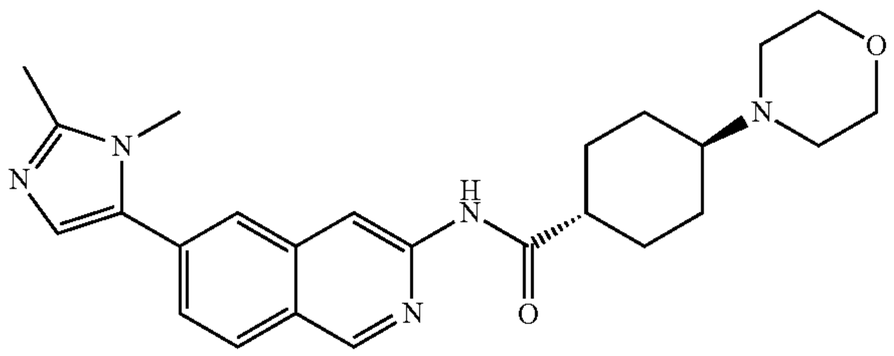
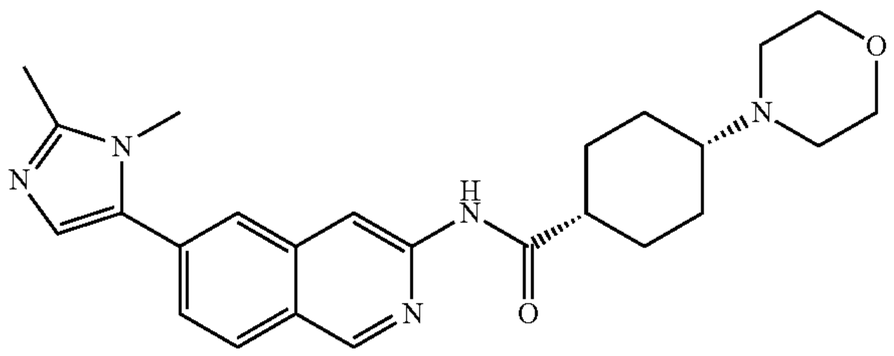
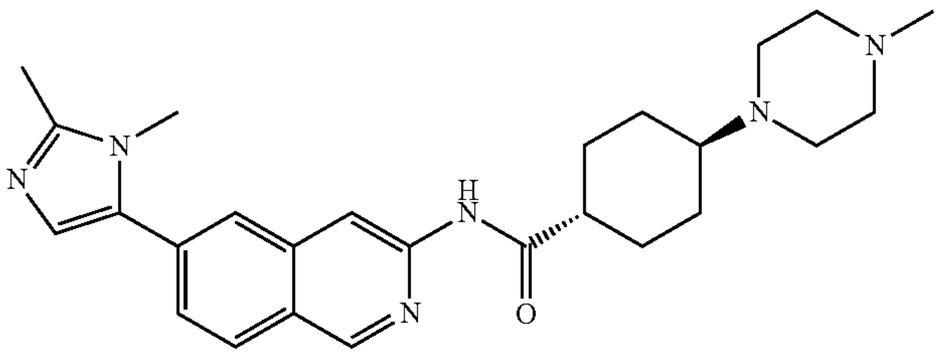
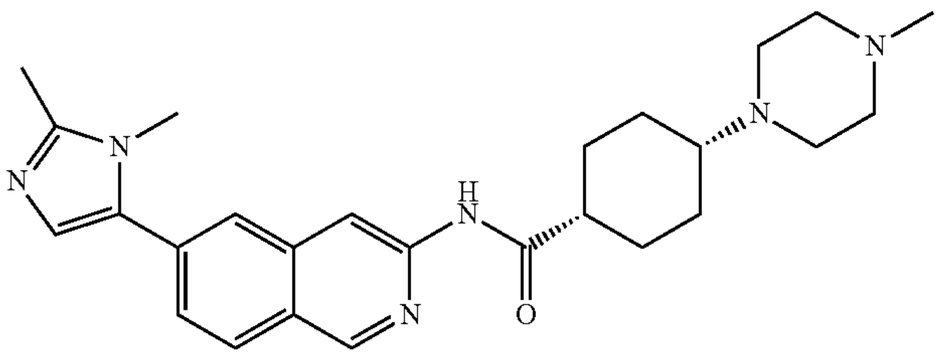
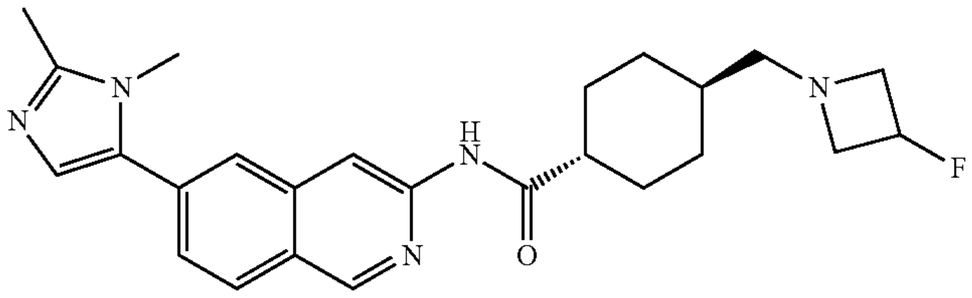
122	
123	
124	
125	
126	
127	
128	

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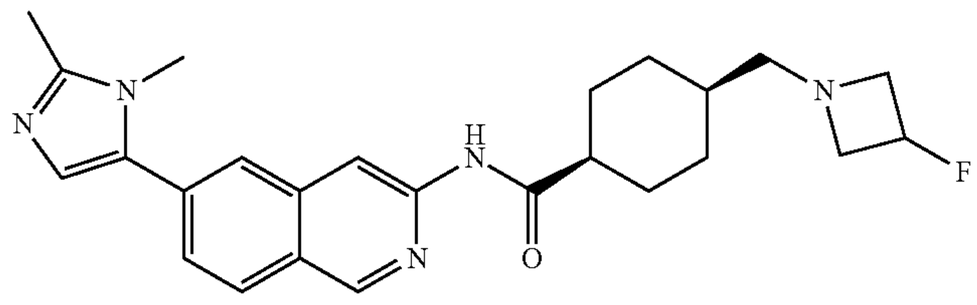

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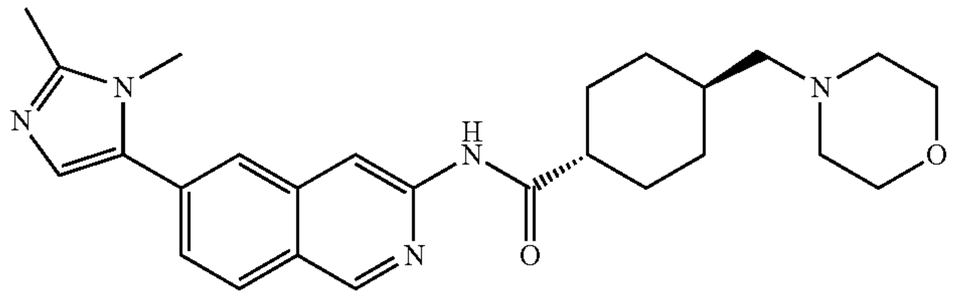

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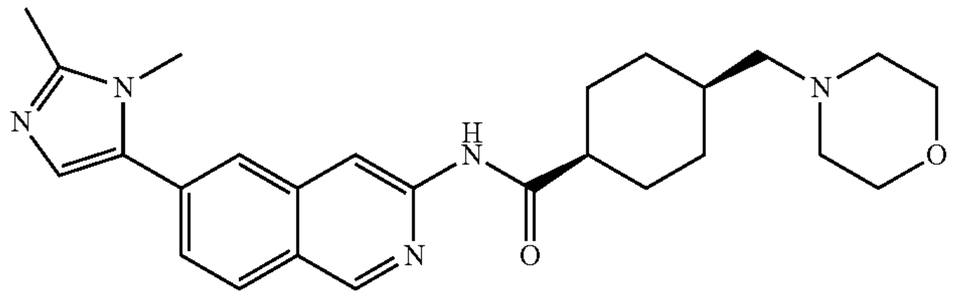

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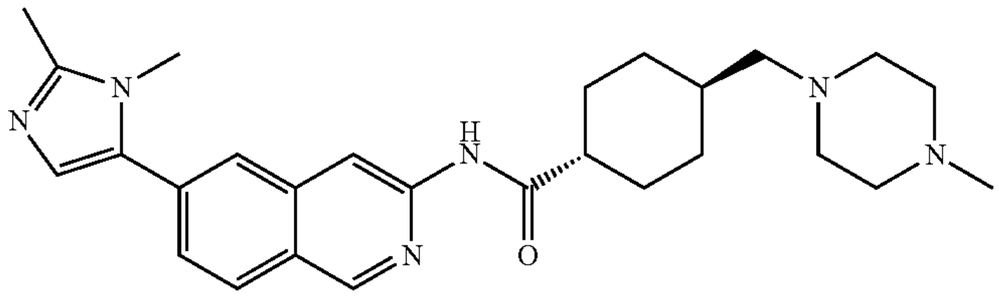

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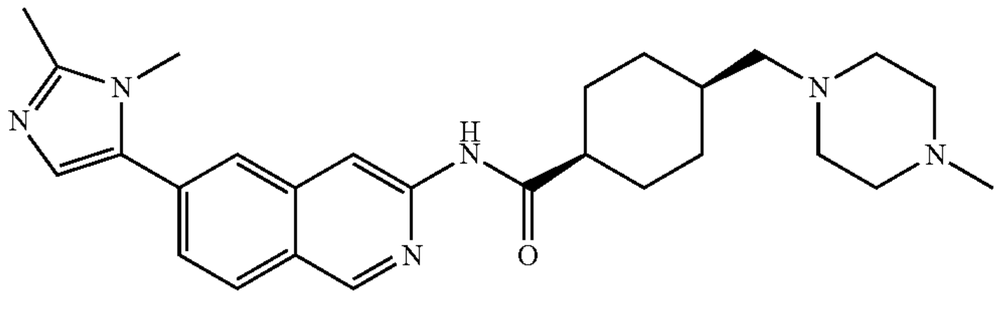

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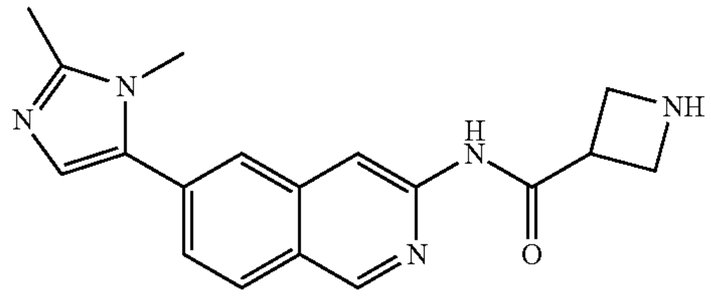

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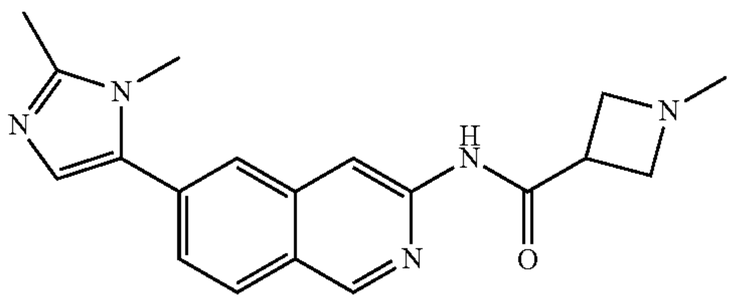

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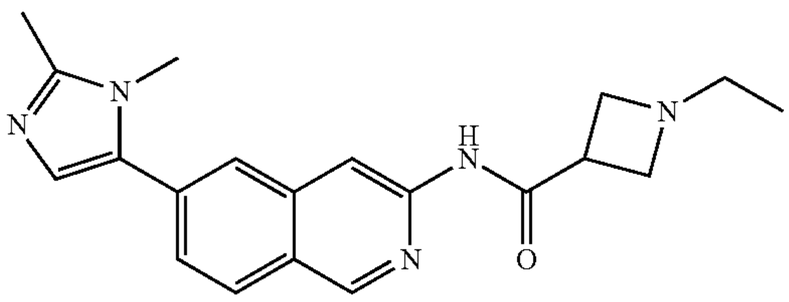

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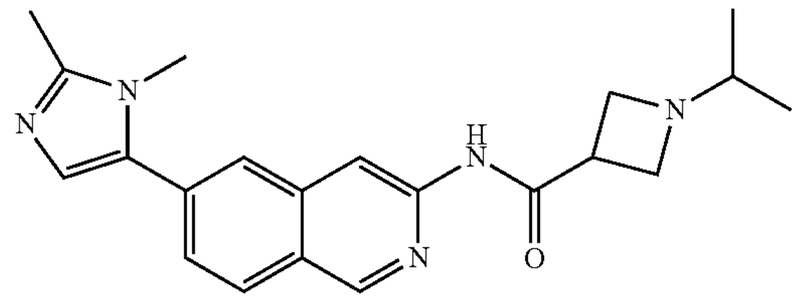
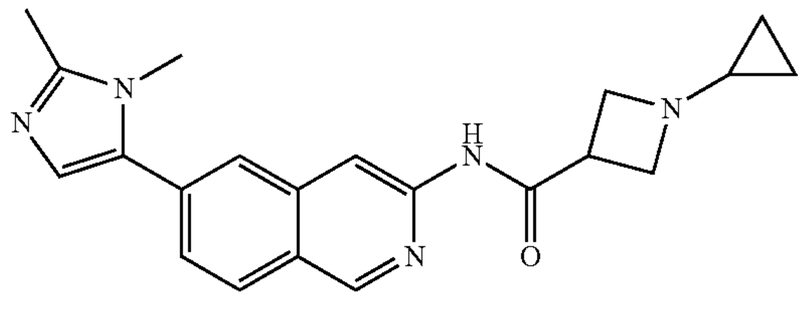
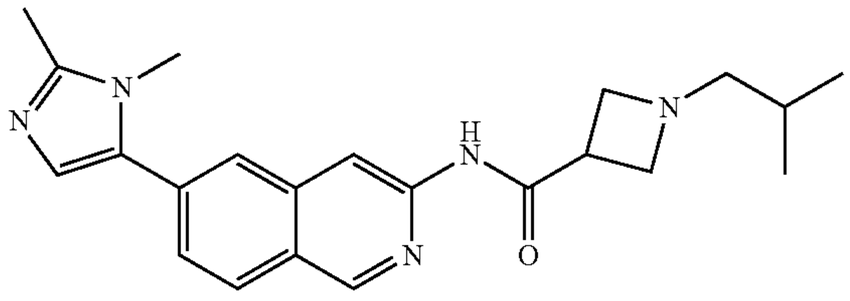
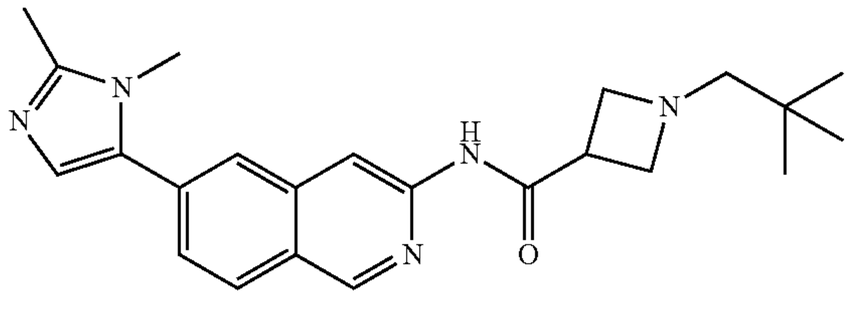
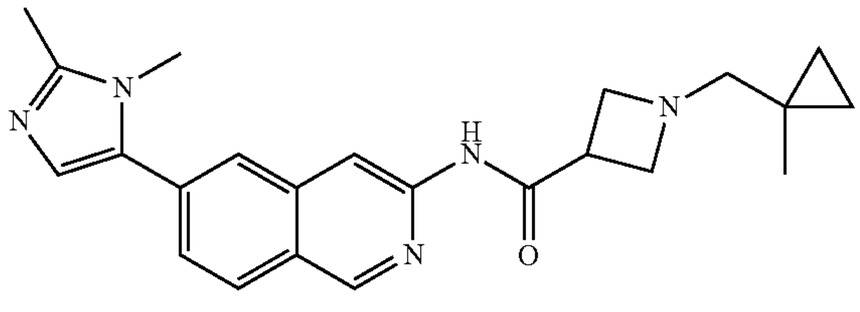
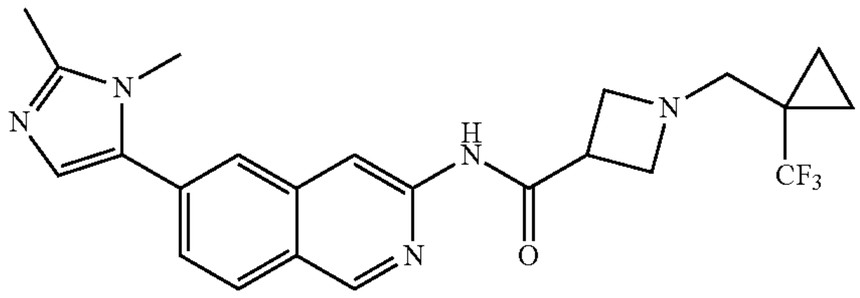
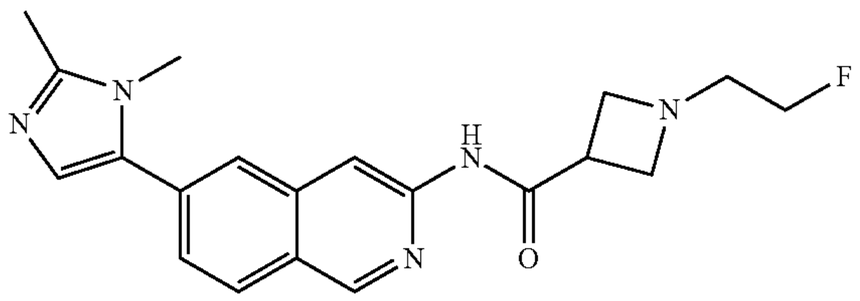
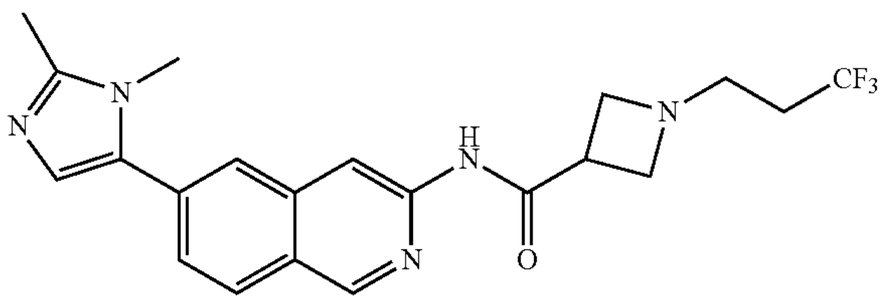
137	
138	
139	
140	
141	
142	
143	
144	

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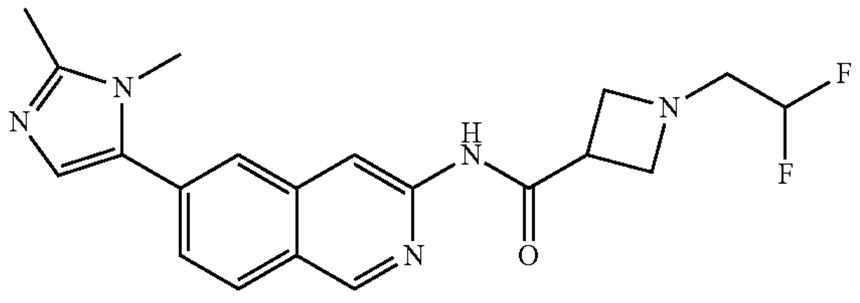
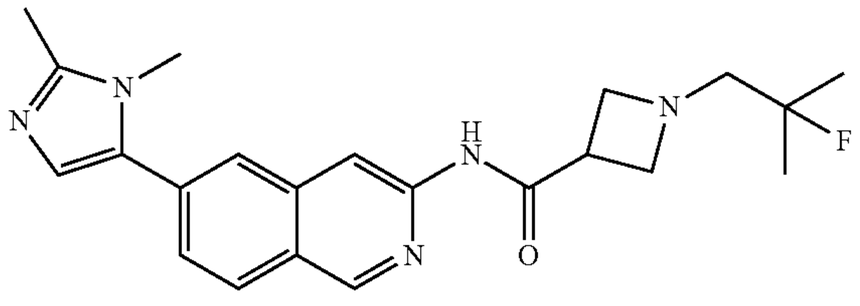
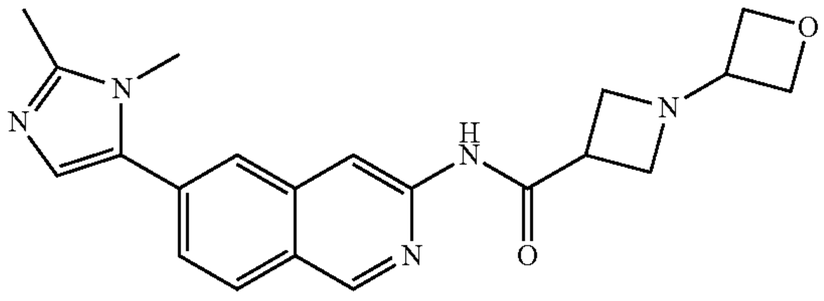
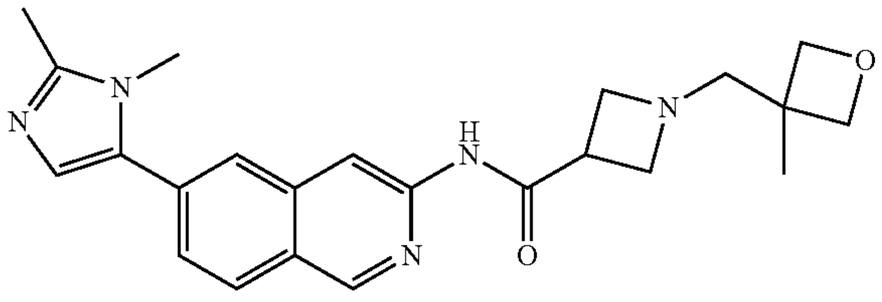
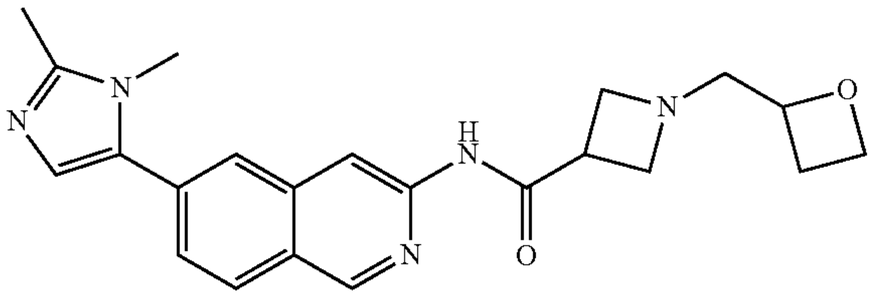
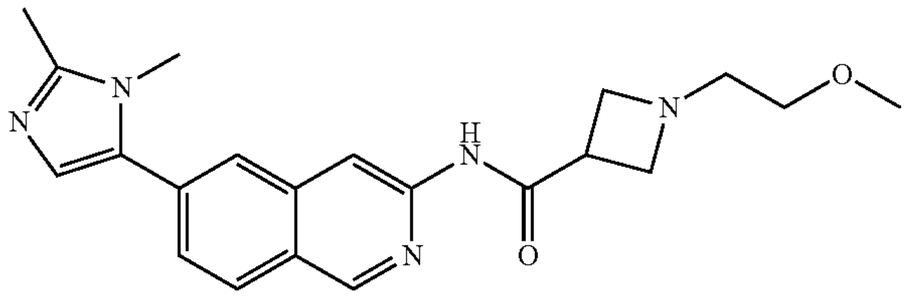
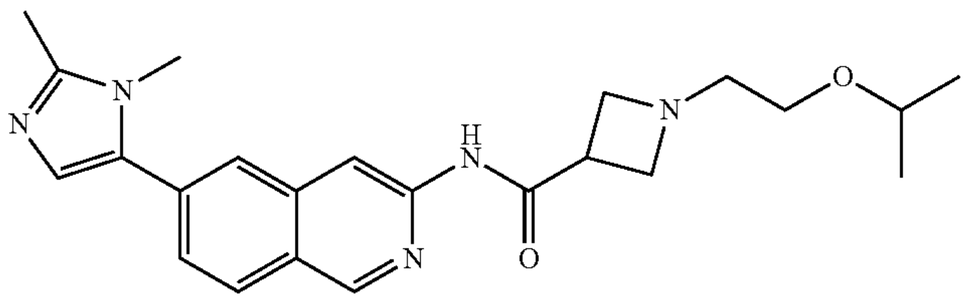
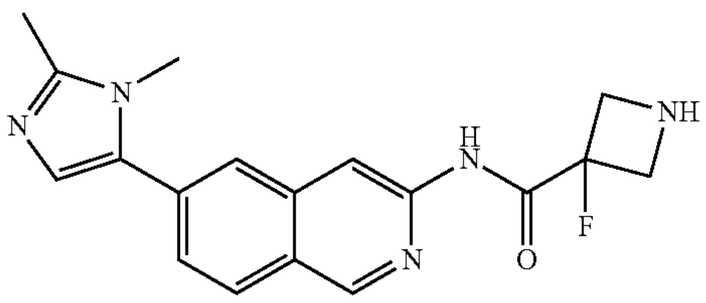
145	
146	
147	
148	
149	
150	
151	
152	

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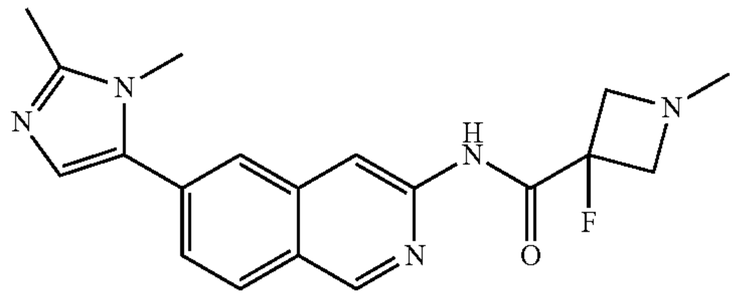
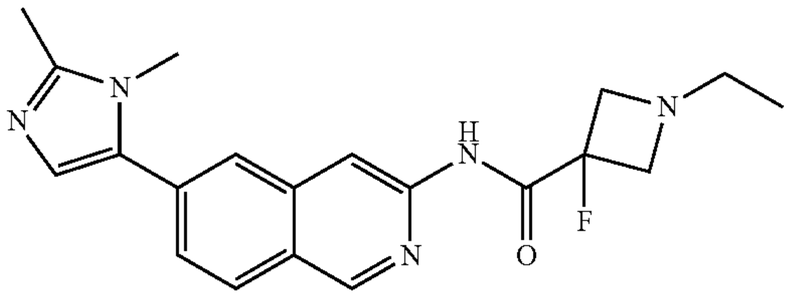
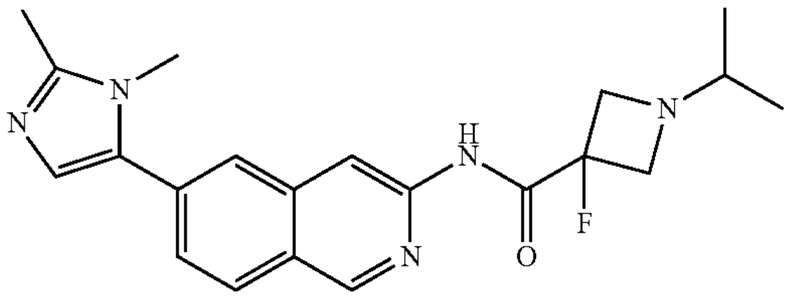
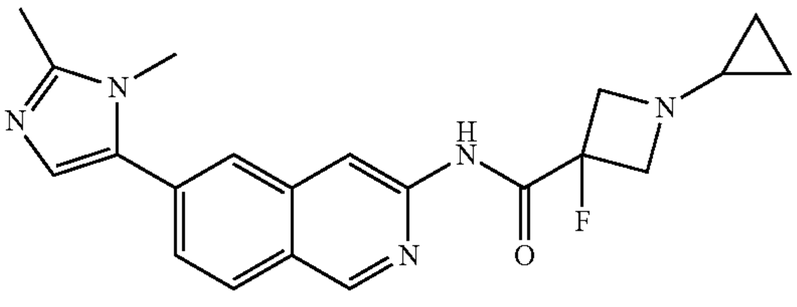
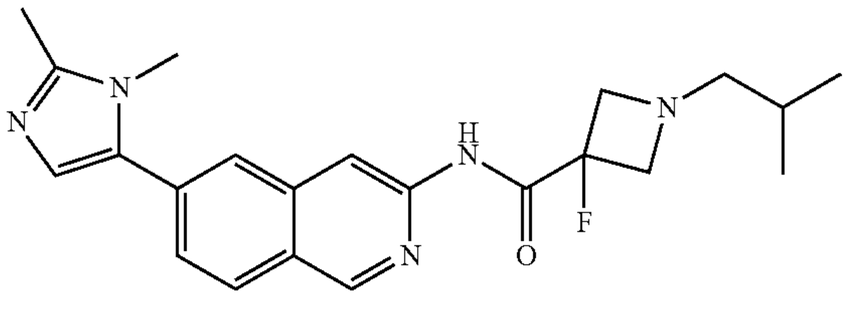
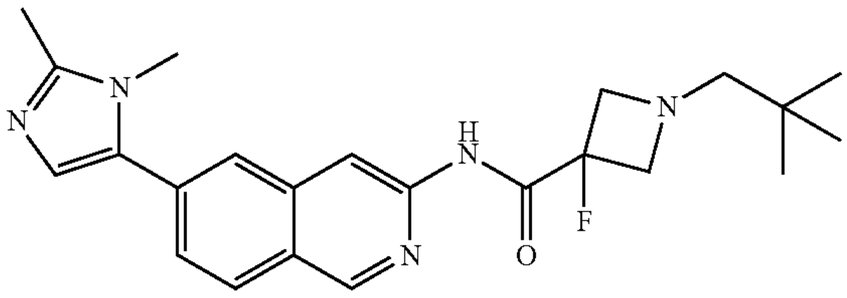
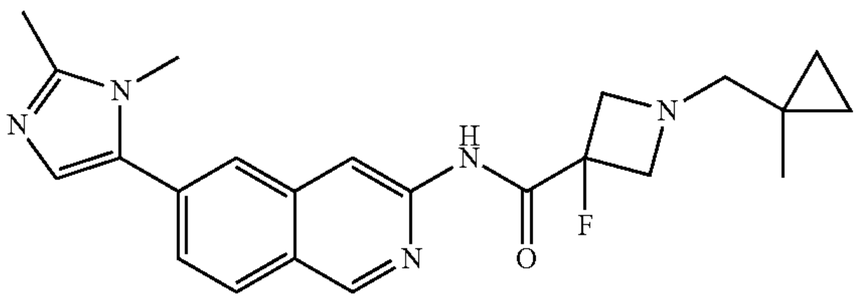
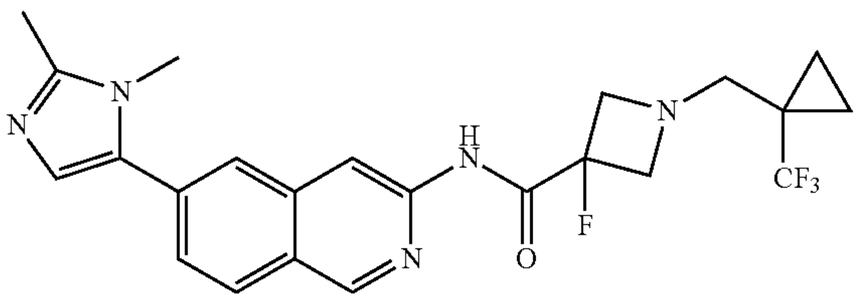
153	
154	
155	
156	
157	
158	
159	
160	

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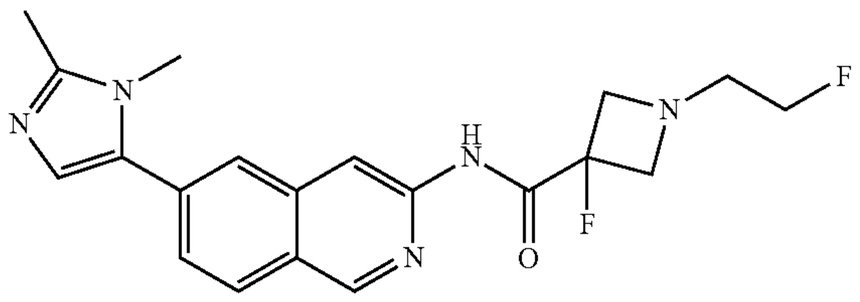
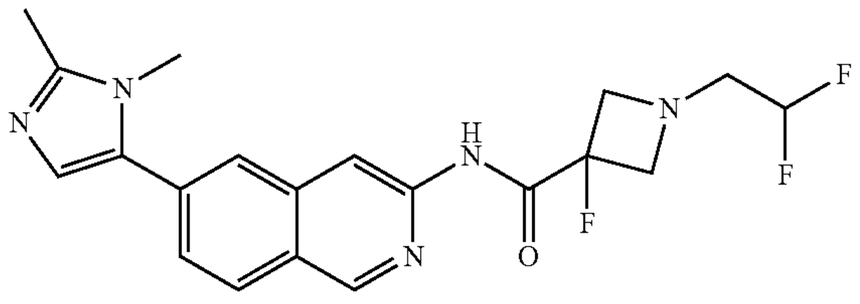
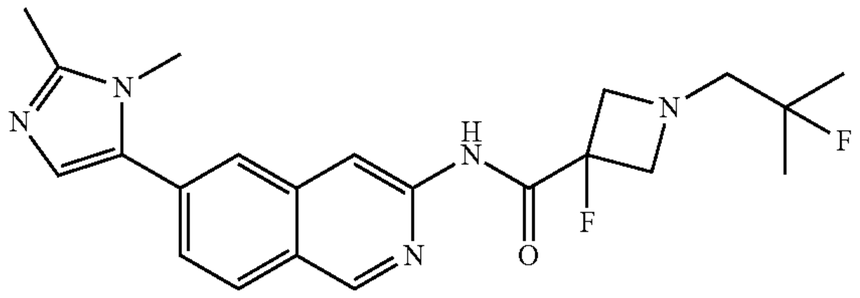
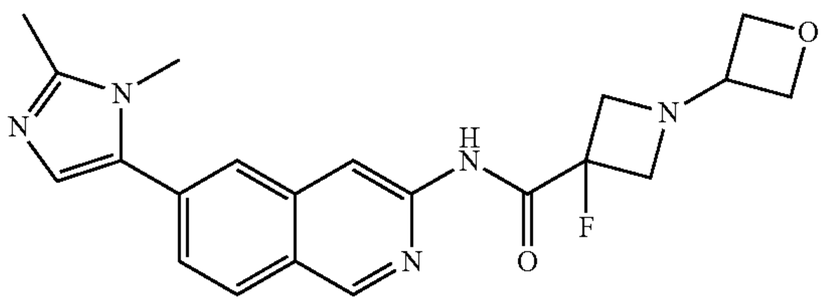
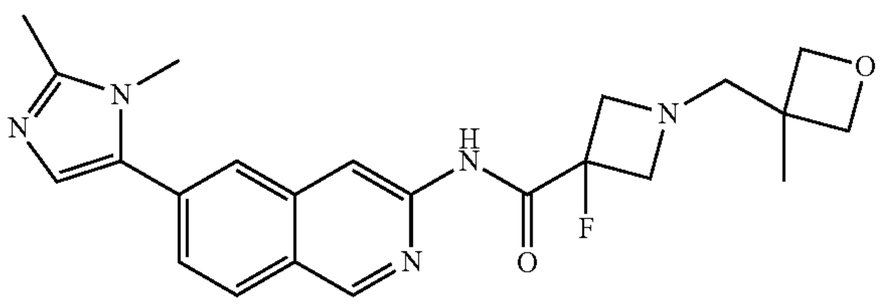
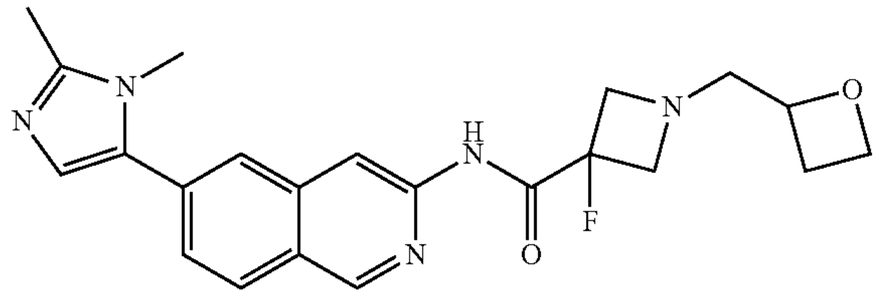
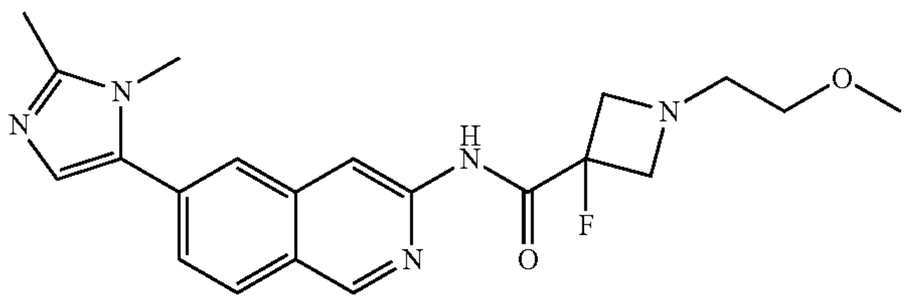
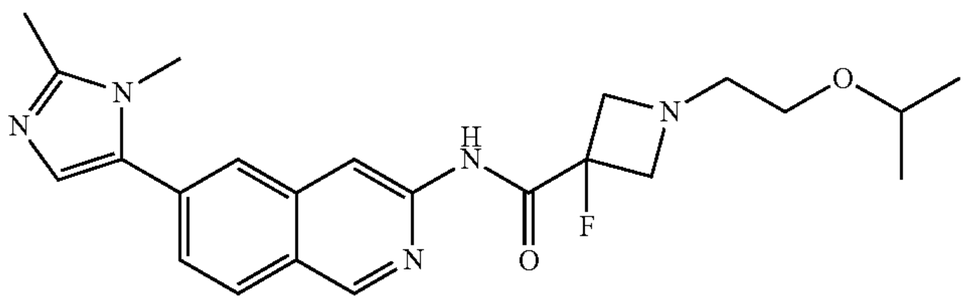
161	
162	
163	
164	
165	
166	
167	
168	

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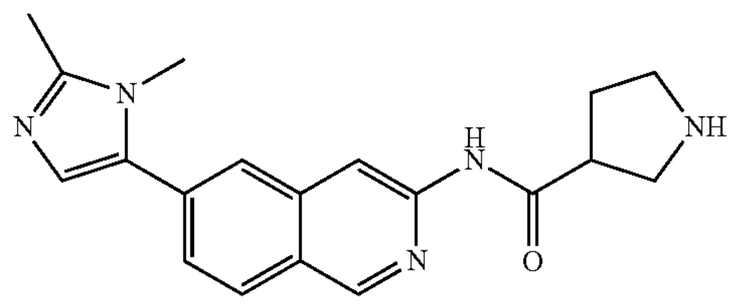
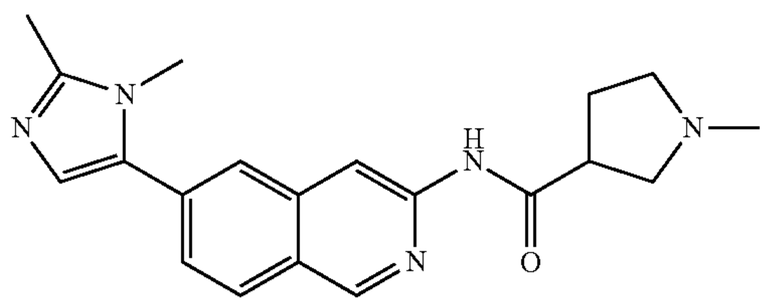
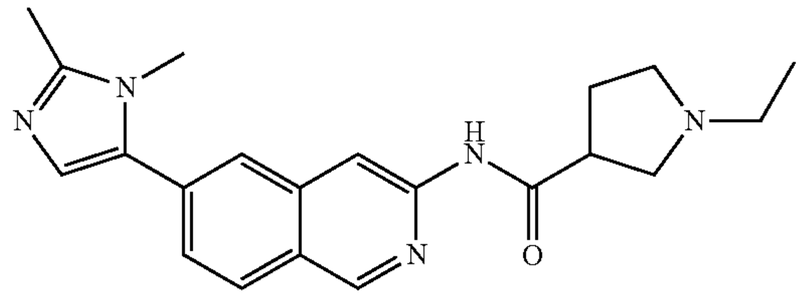
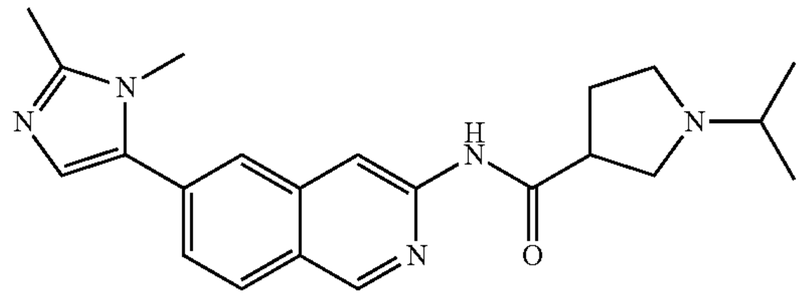
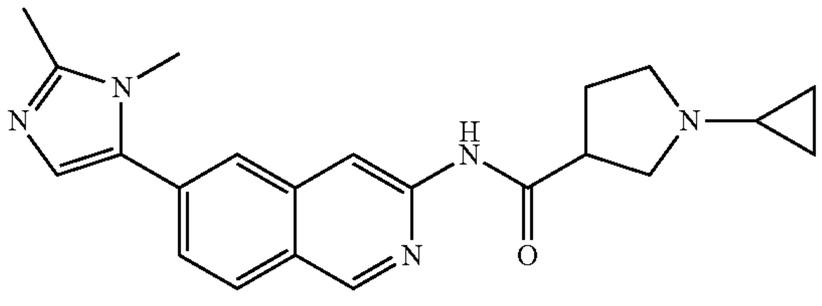
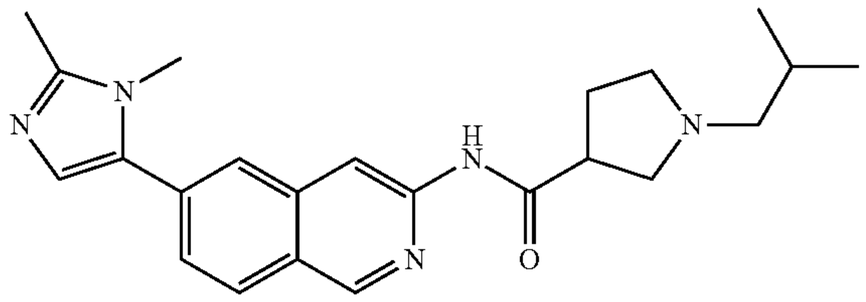
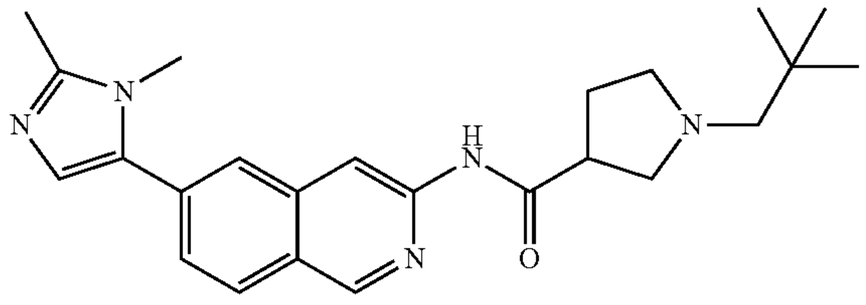
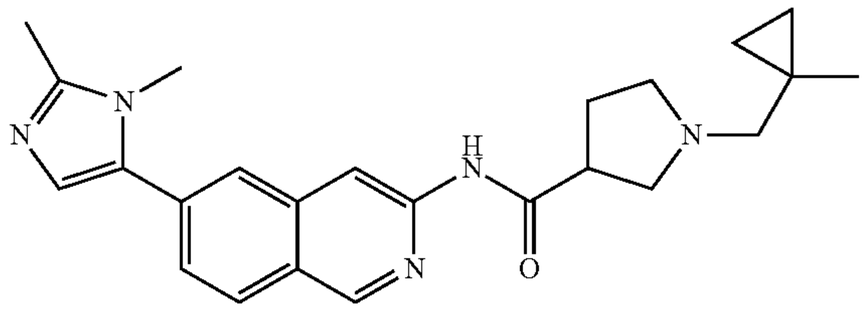
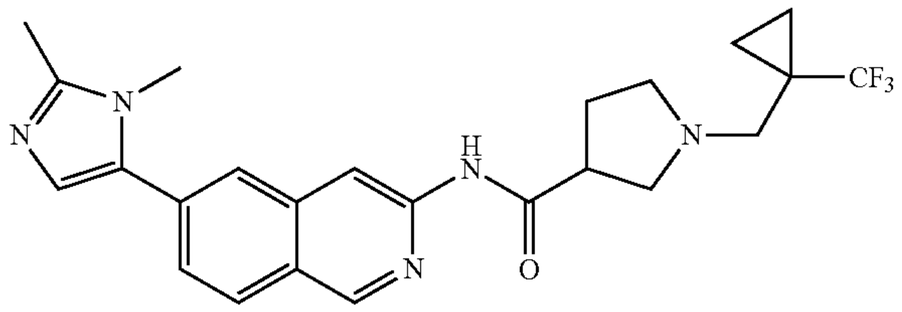
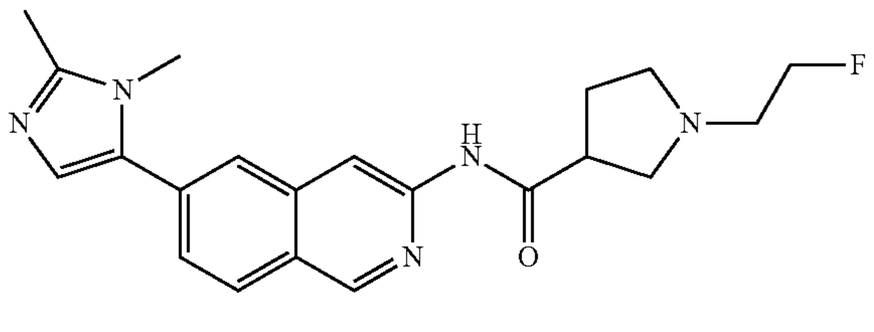
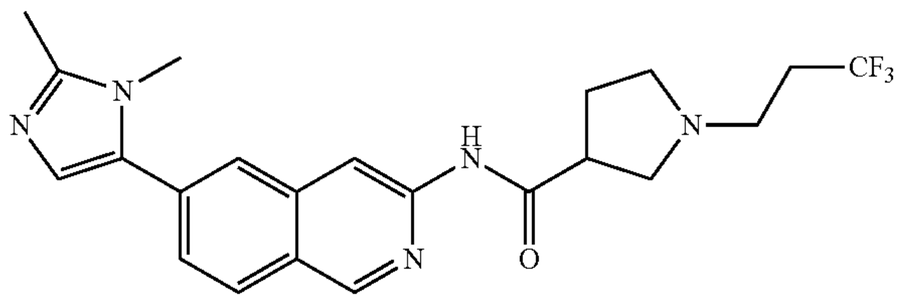
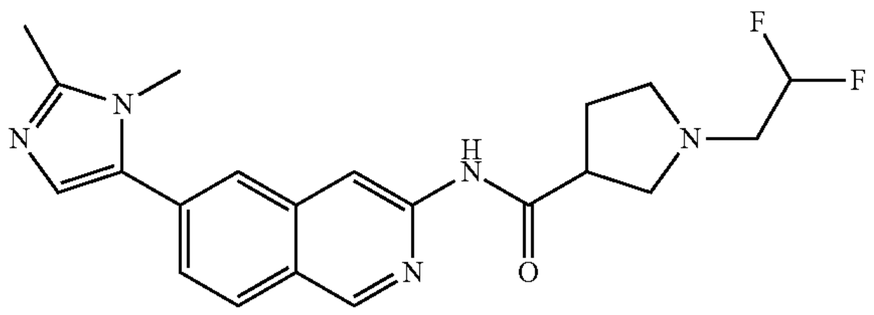
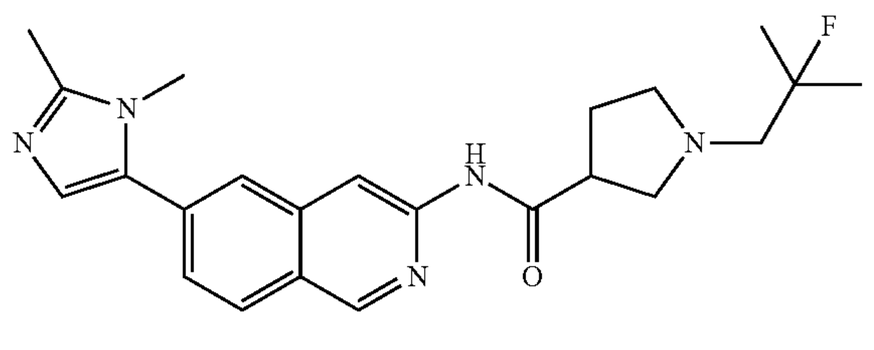
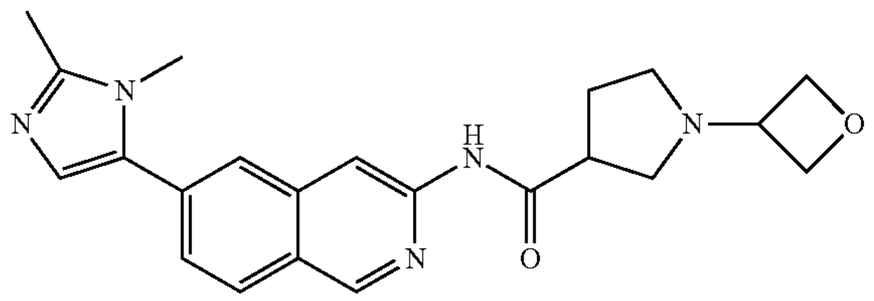
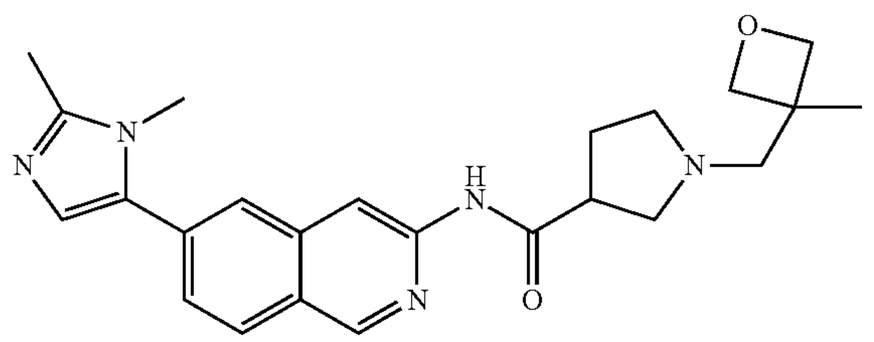
169	
170	
171	
172	
173	
174	
175	
176	

TABLE 1-continued

177	
178	
179	
180	
181	
182	
183	

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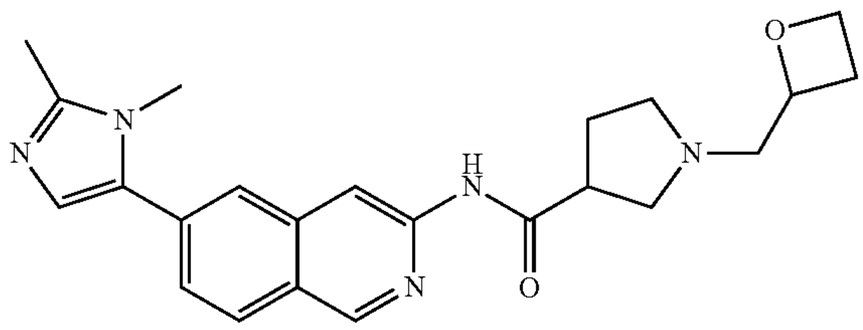

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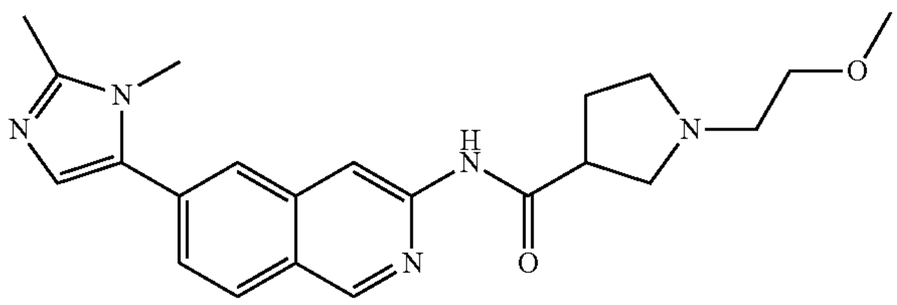

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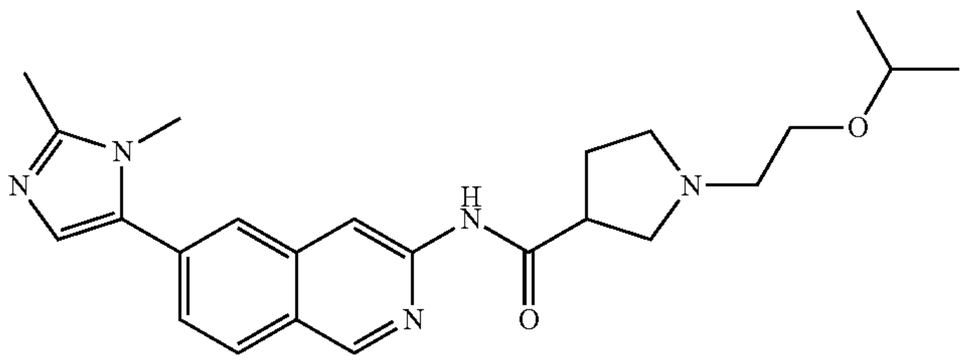

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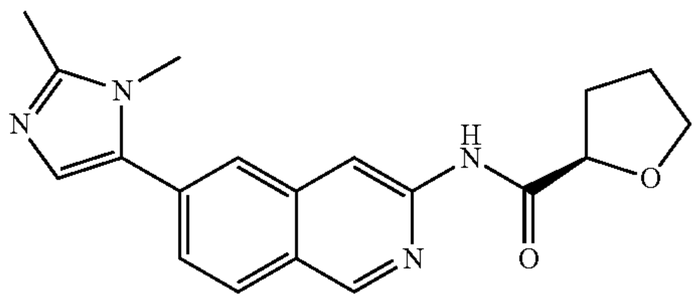

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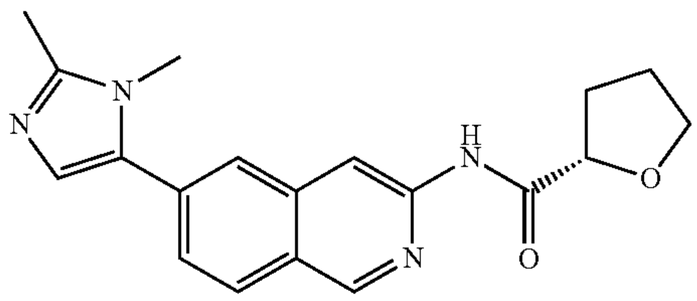

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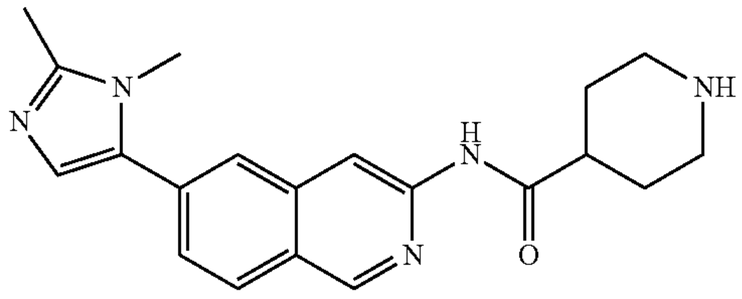

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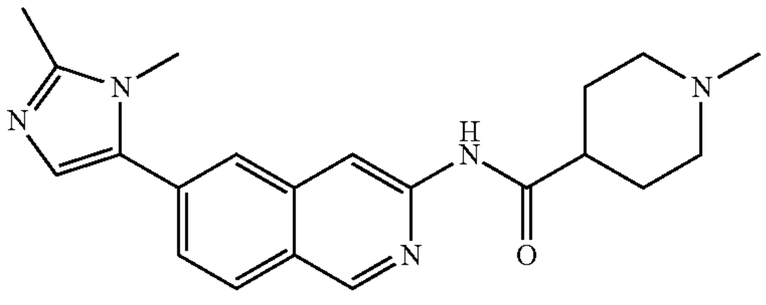

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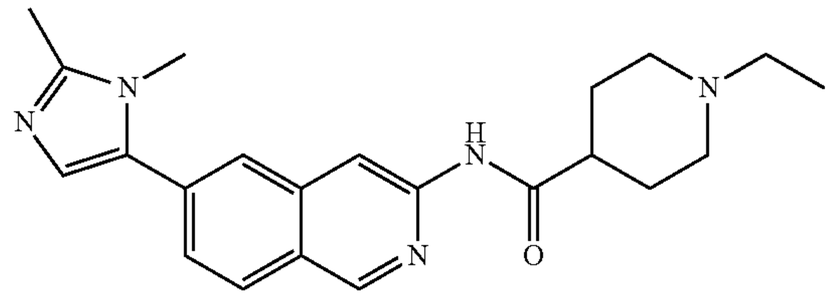
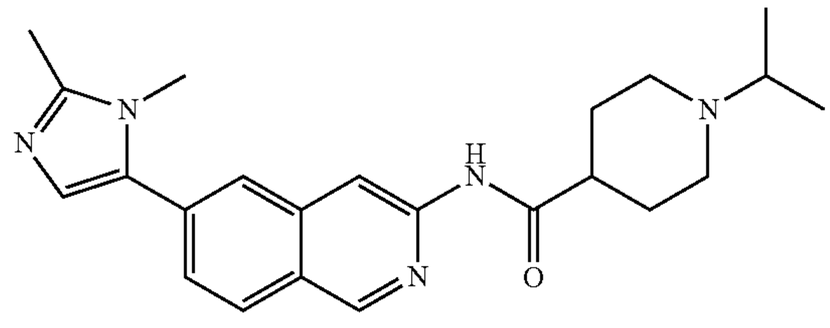
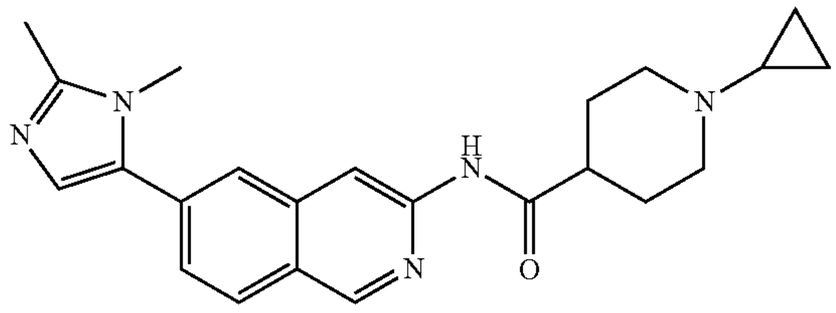
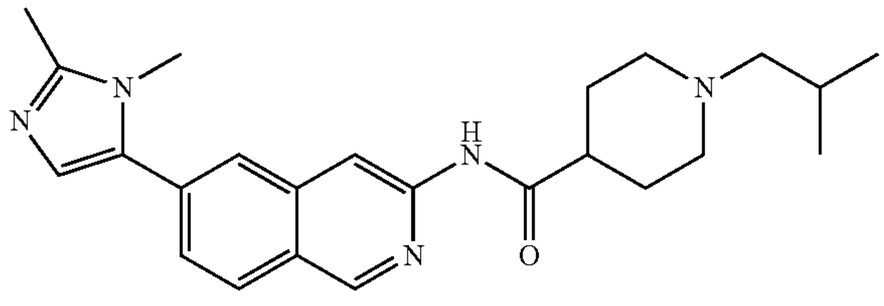
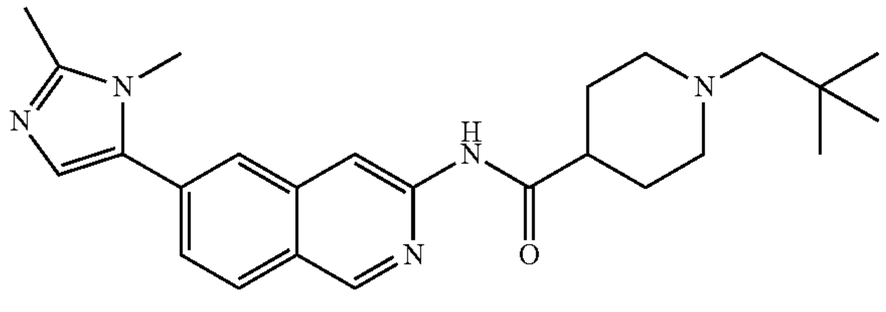
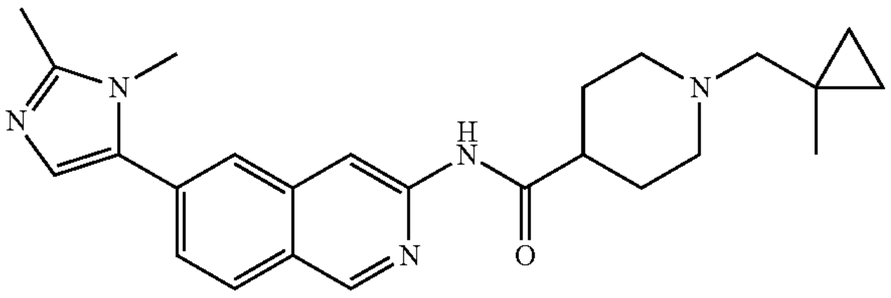
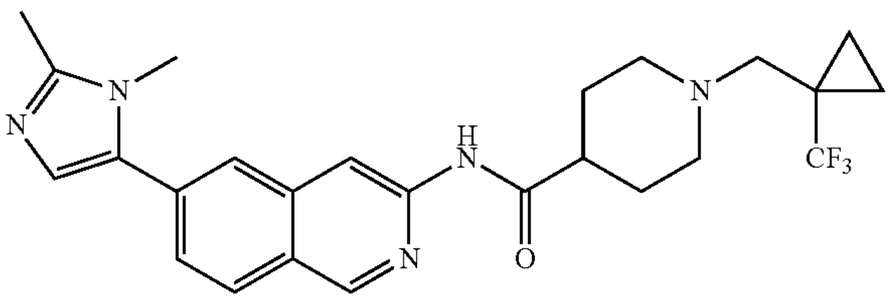
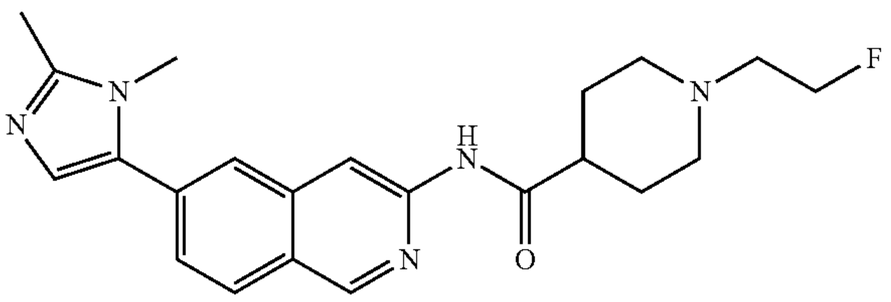
	191 
	192 
	193 
	194 
	195 
	196 
	197 
	198 

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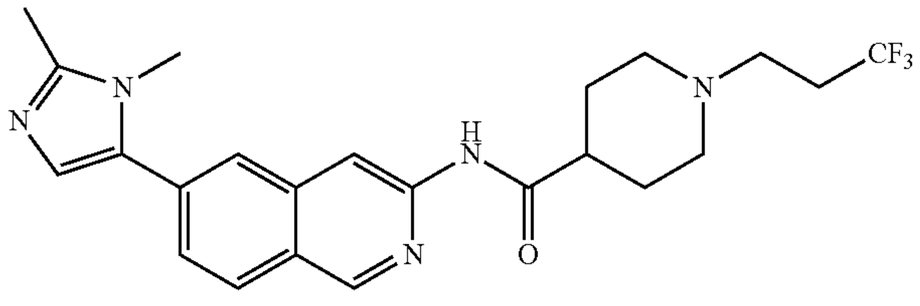
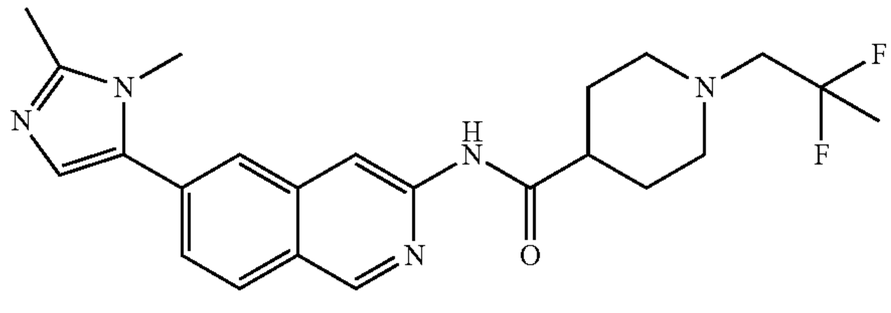
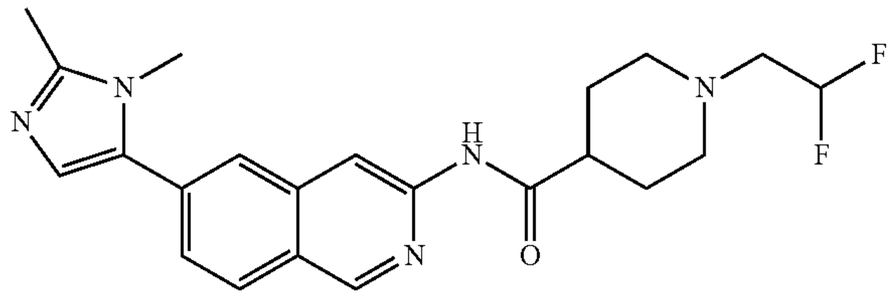
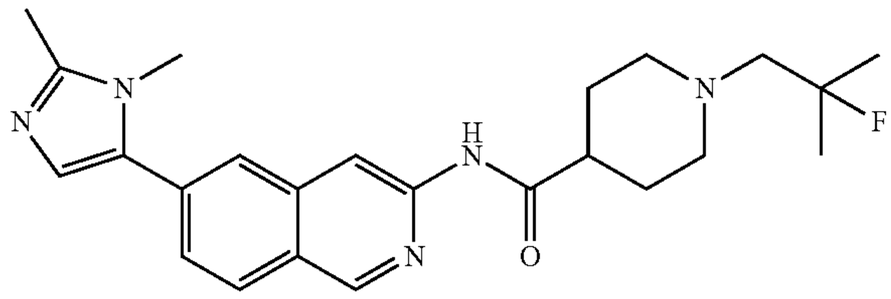
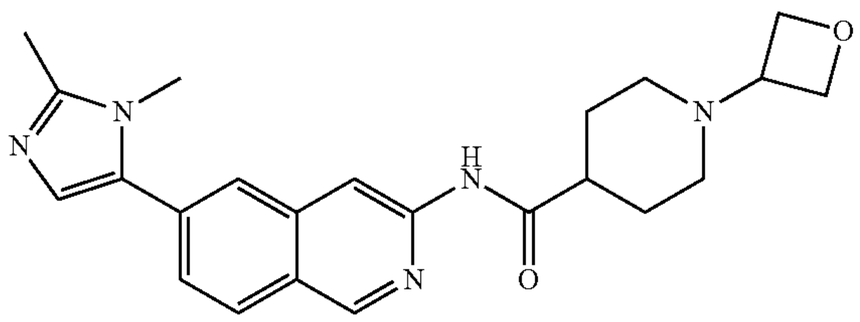
199	
200	
201	
202	
203	
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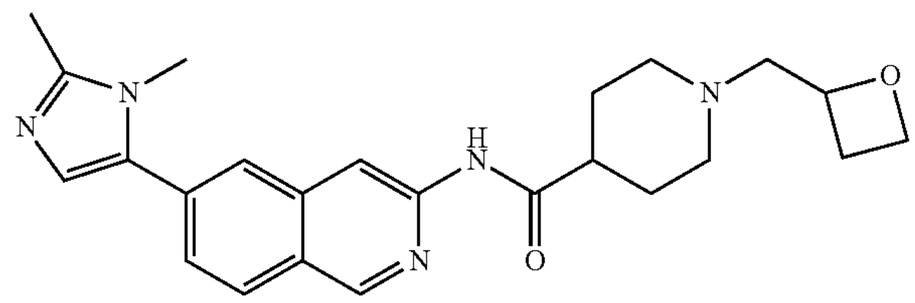
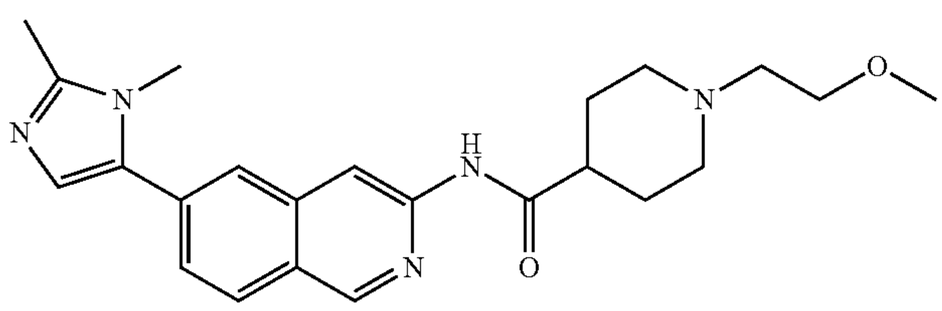
205	
206	

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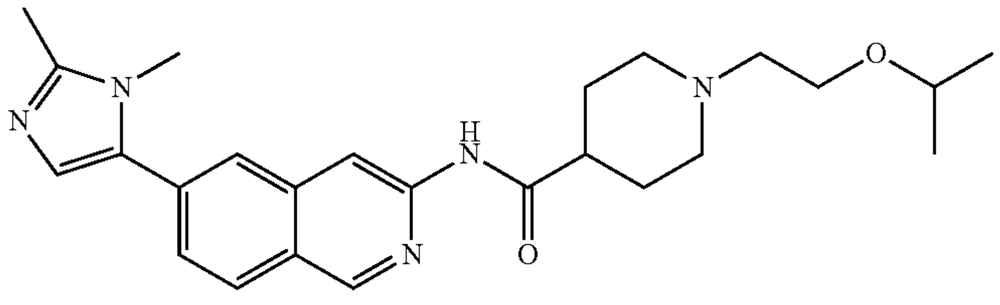
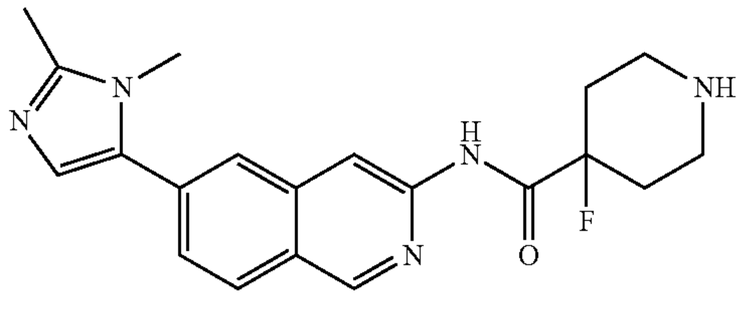
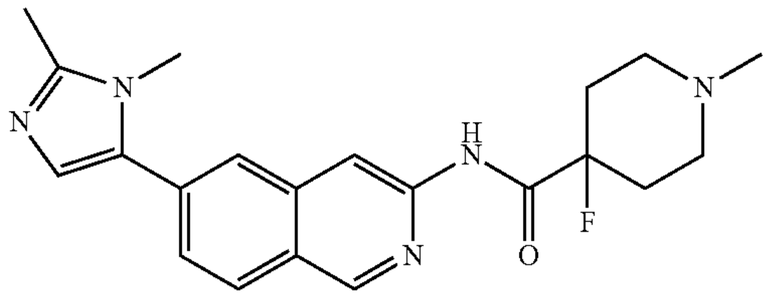
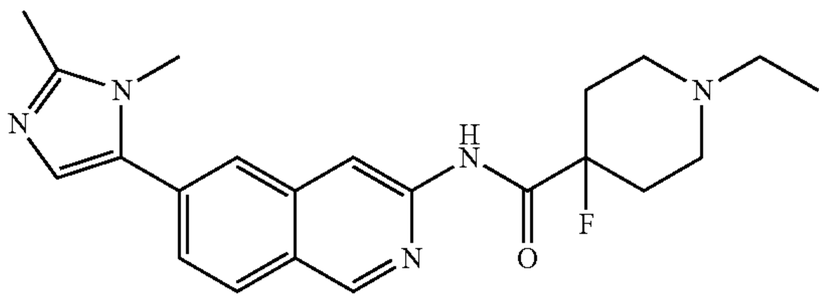
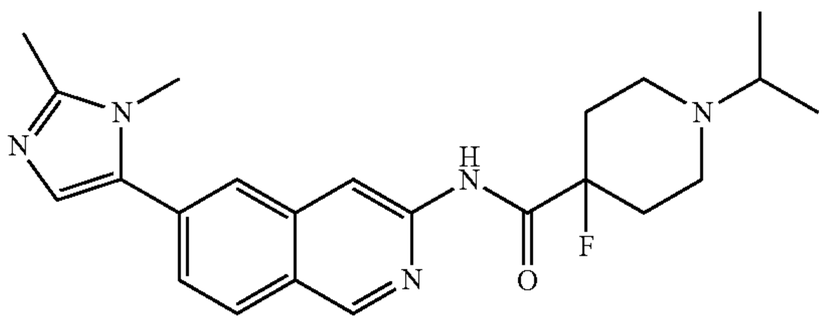
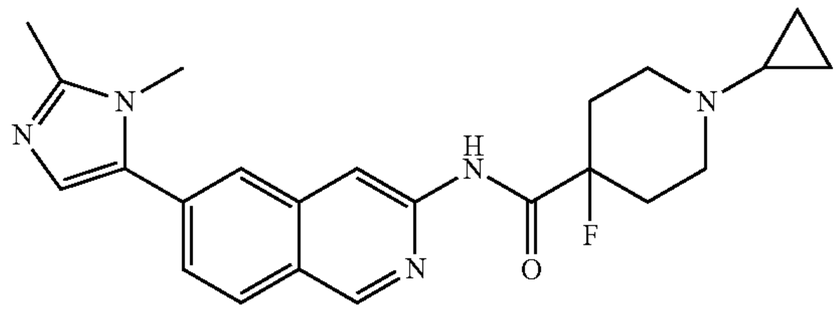
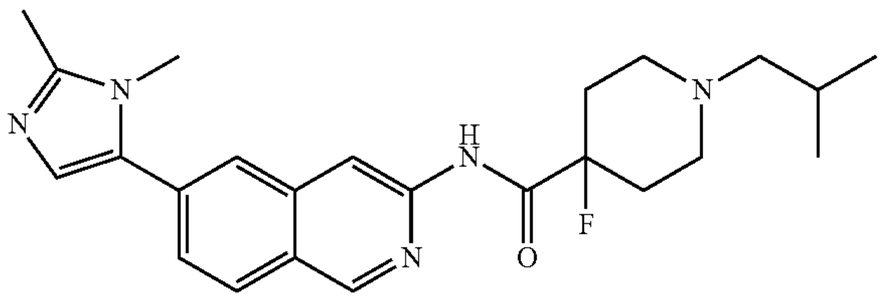
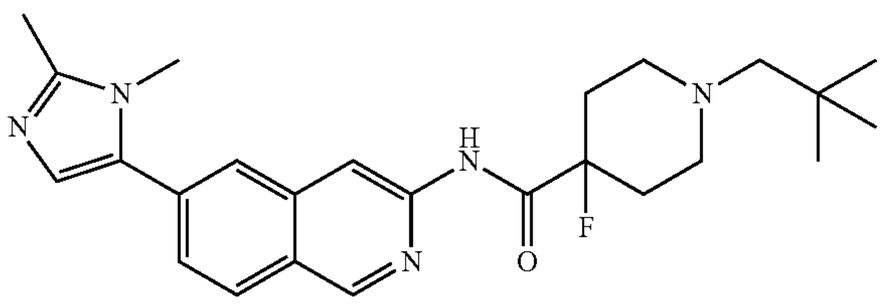
207	
208	
209	
210	
211	
212	
213	
214	

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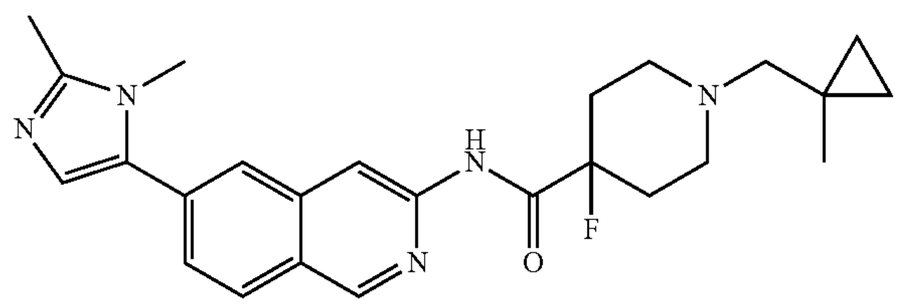
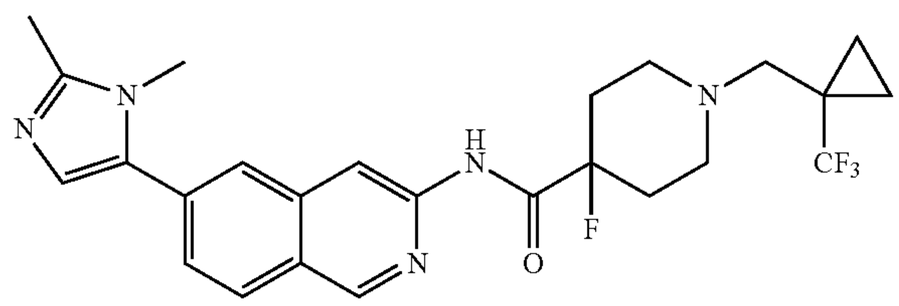
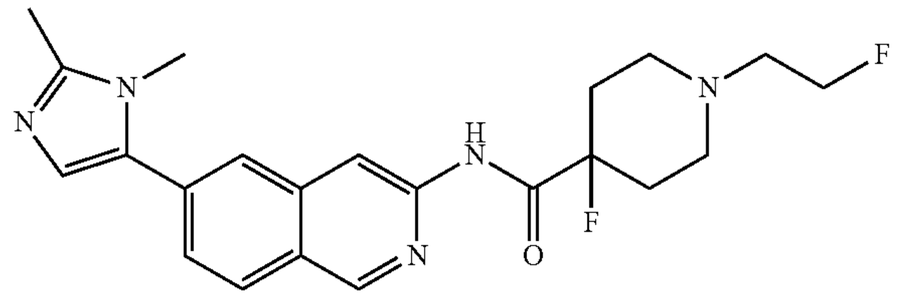
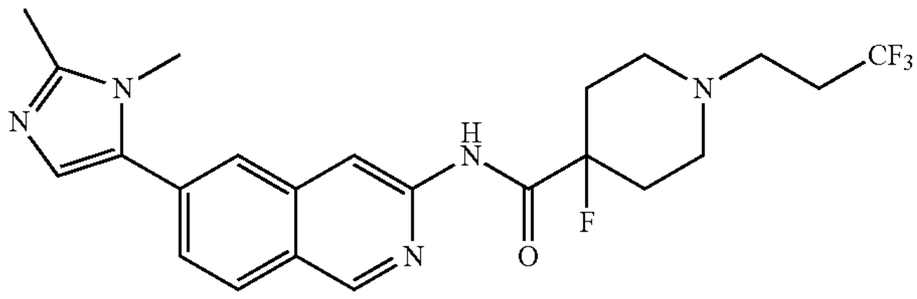
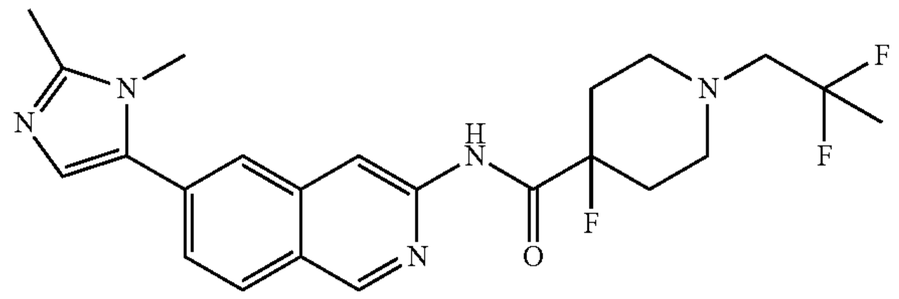
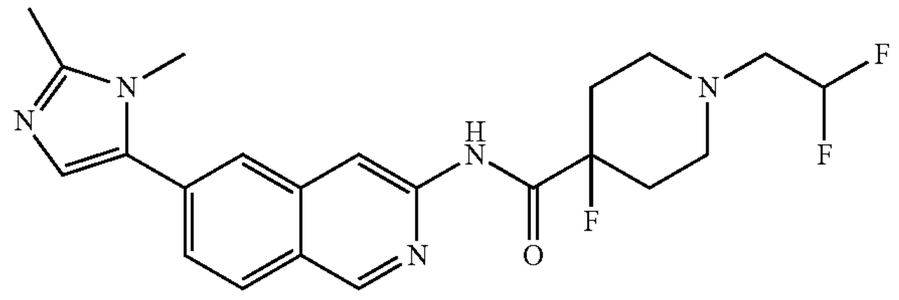
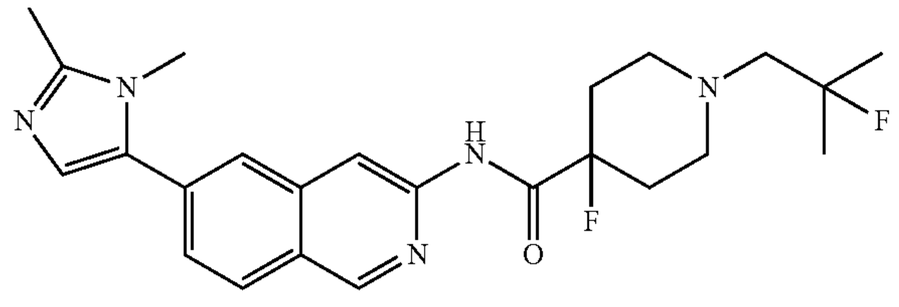
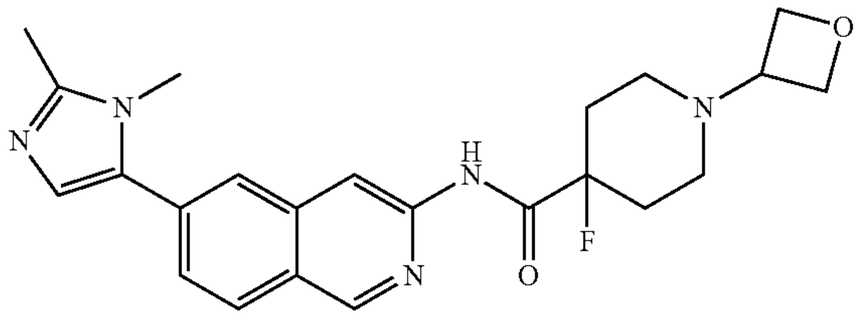
215	
216	
217	
218	
219	
220	
221	
222	

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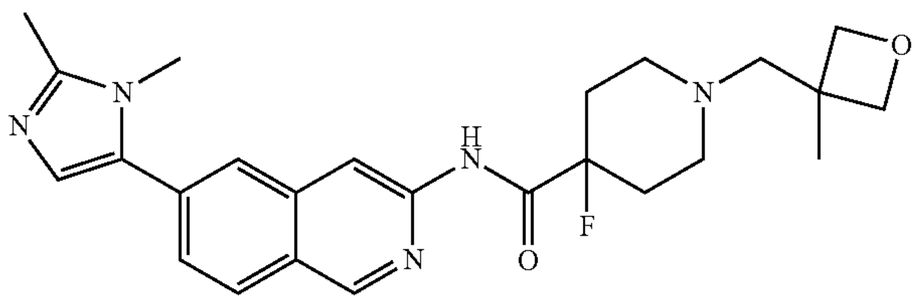
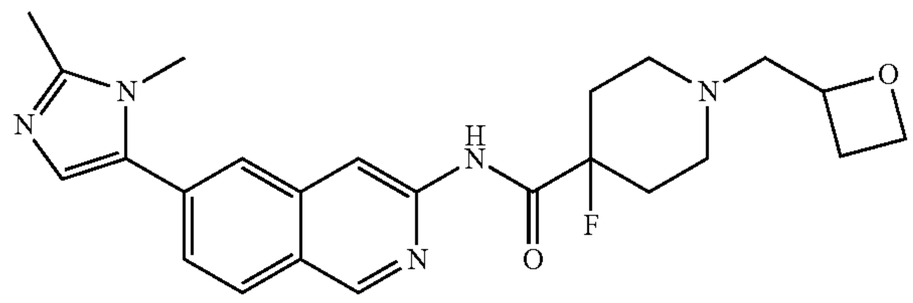
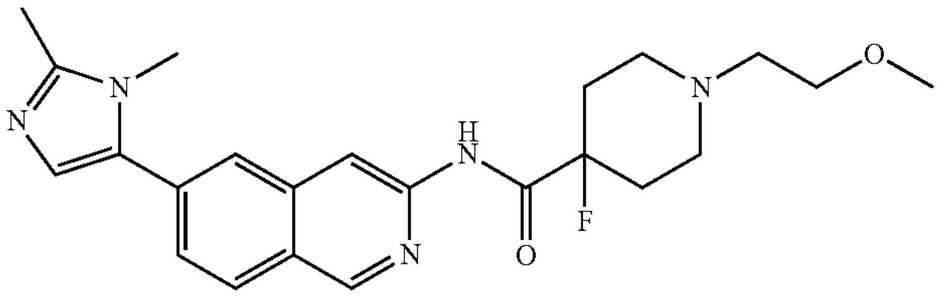
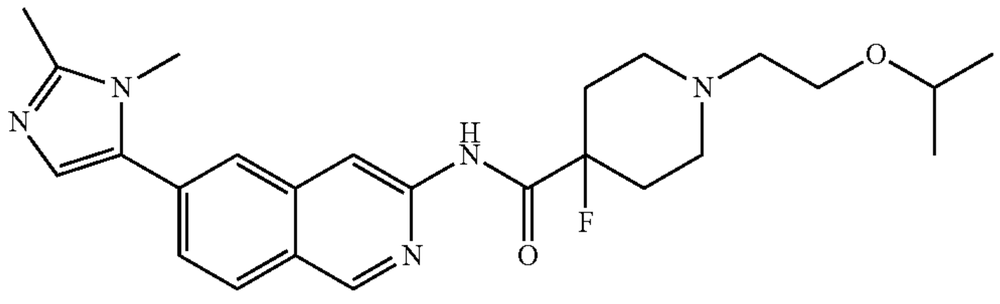
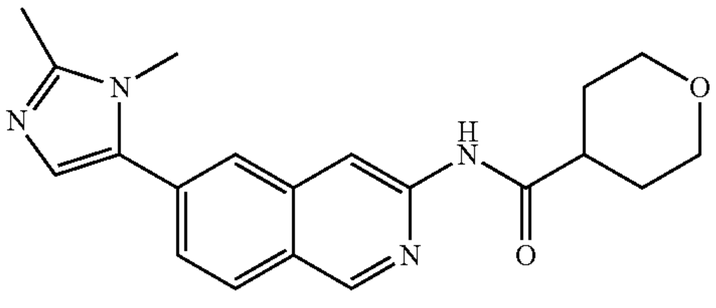
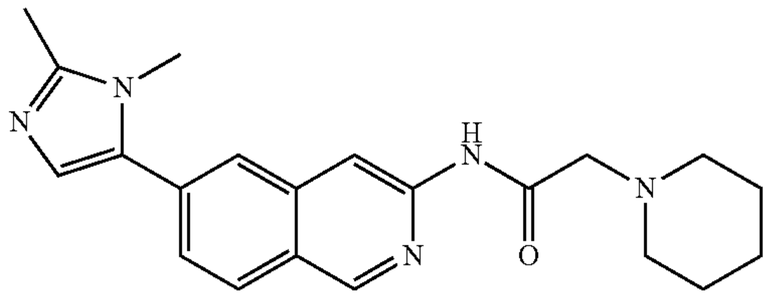
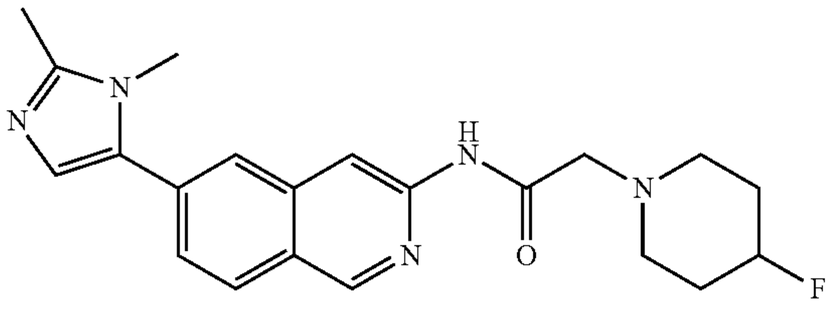
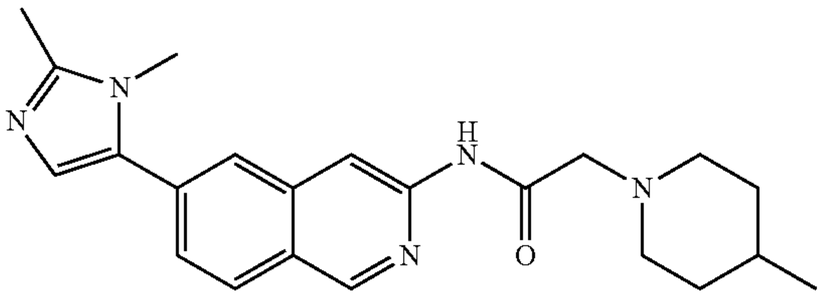
	223
	224
	225
	226
	227
	228
	229
	230

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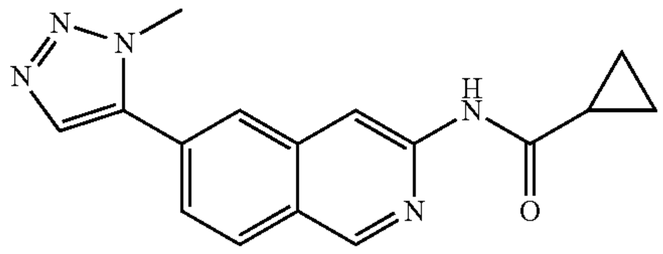
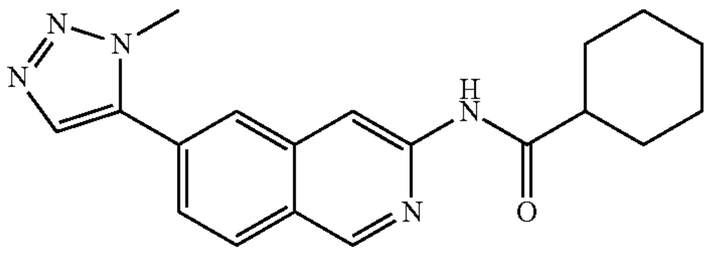
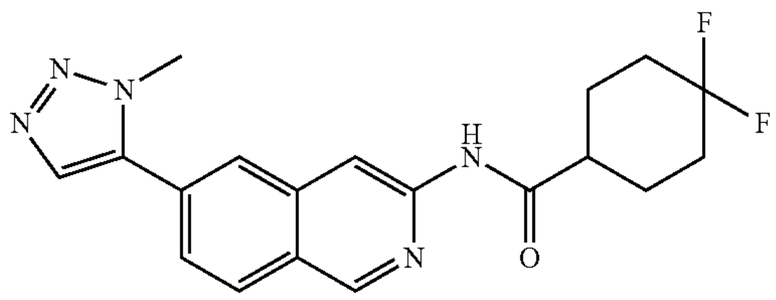
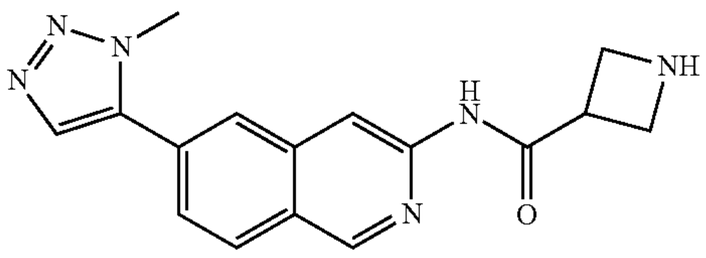
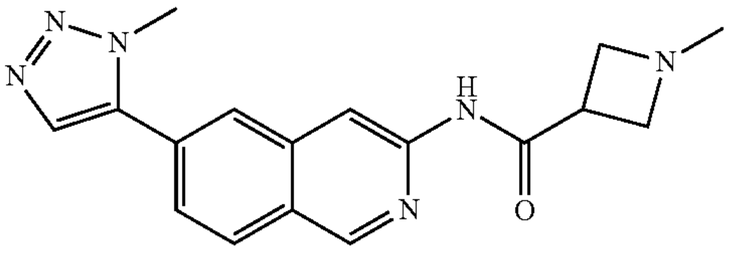
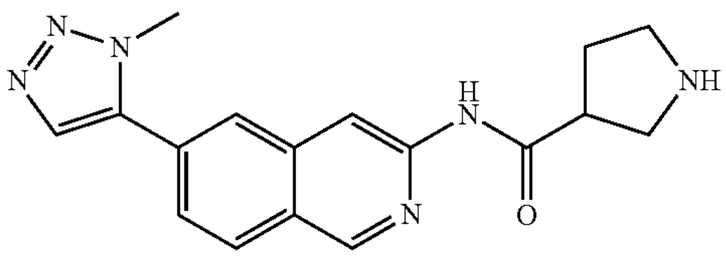
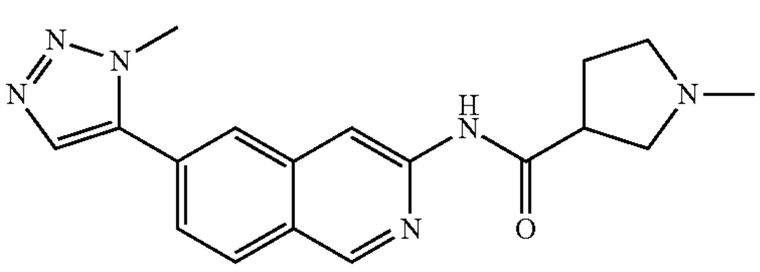
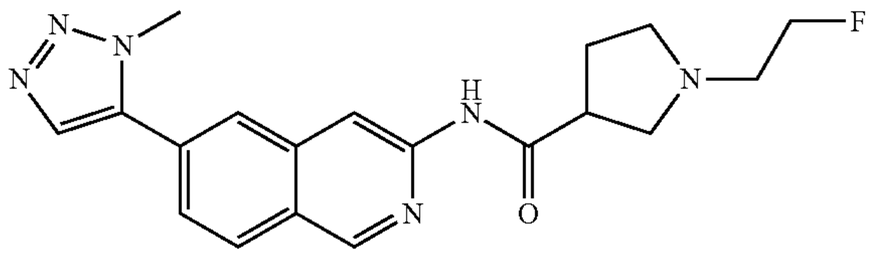
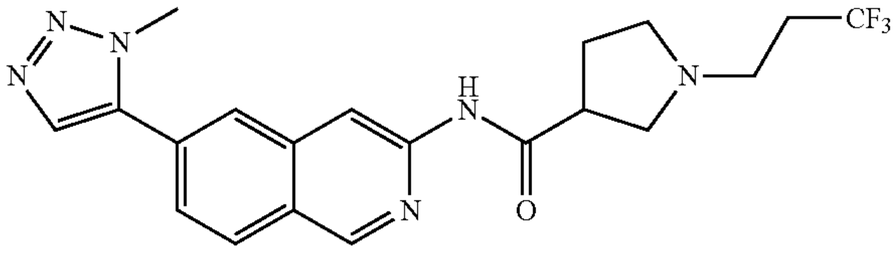
	231
	232
	233
	234
	235
	236
	237
	238
	239

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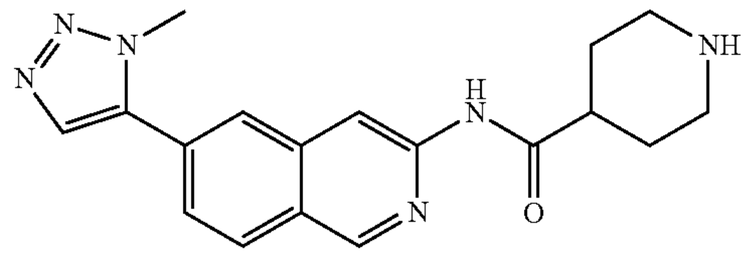
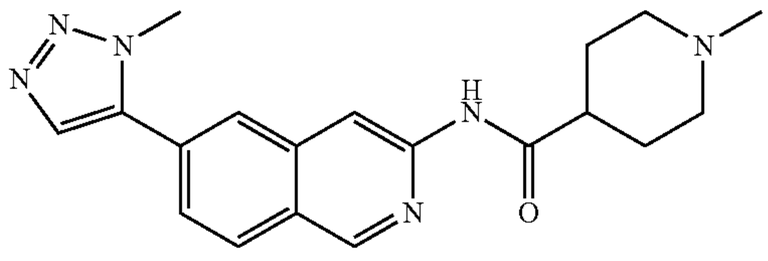
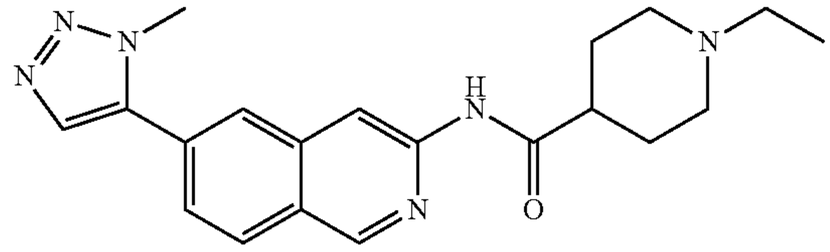
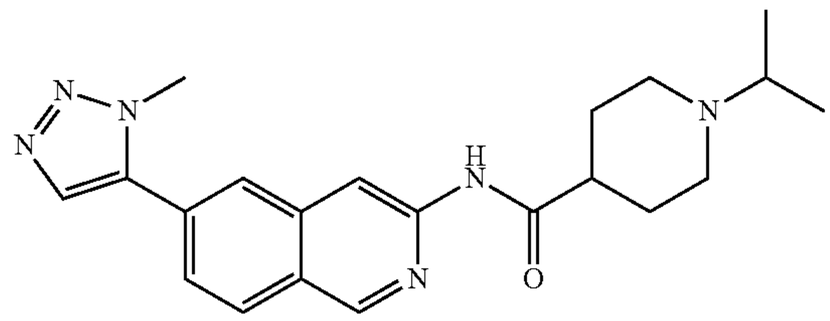
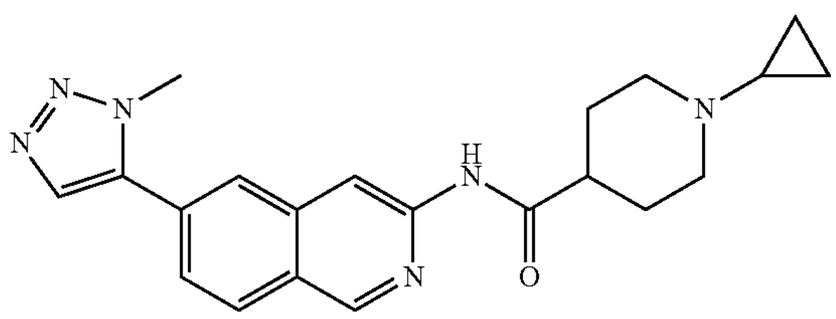
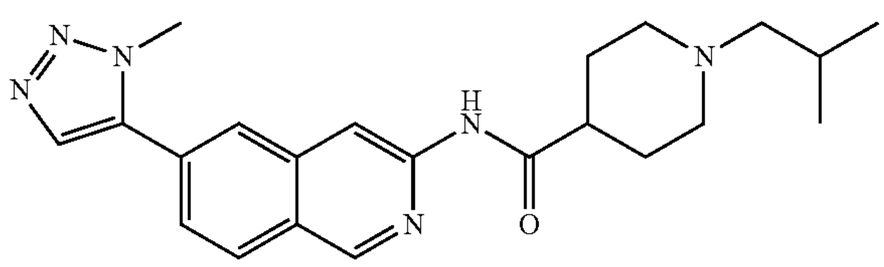
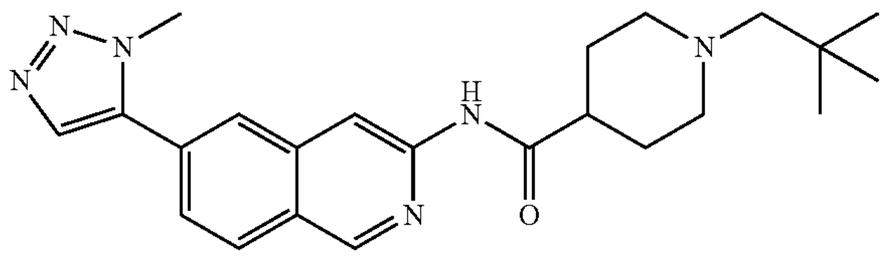
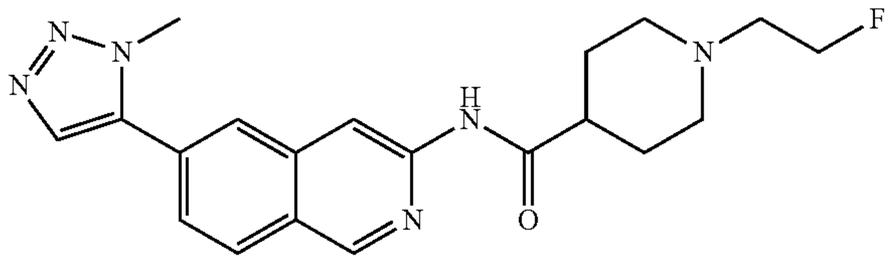
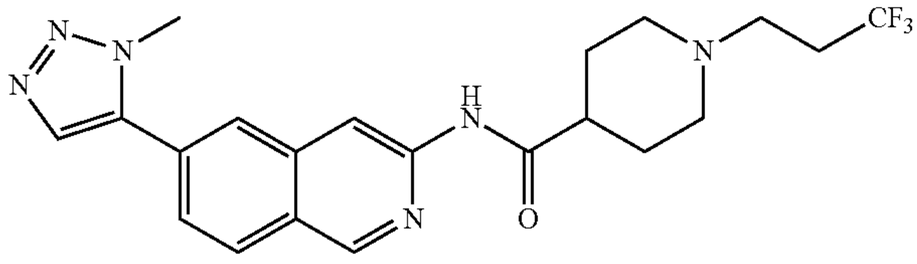
	240
	241
	242
	243
	244
	245
	246
	247
	248

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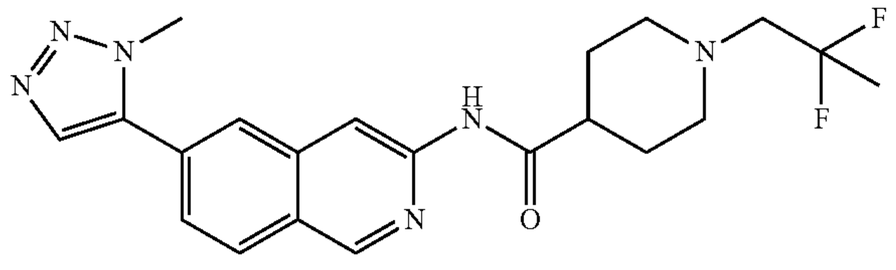
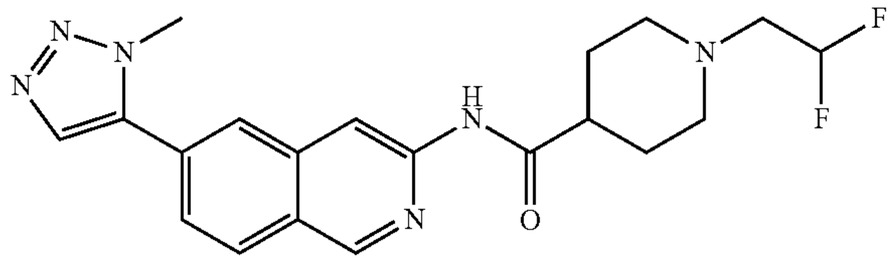
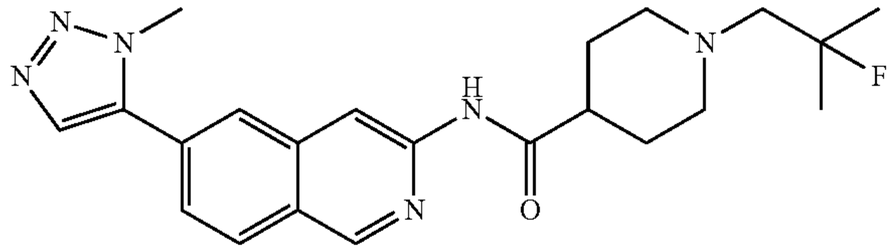
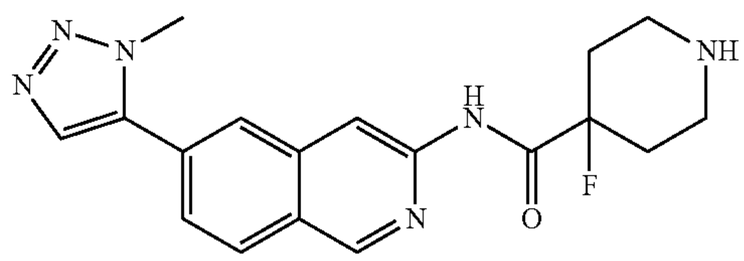
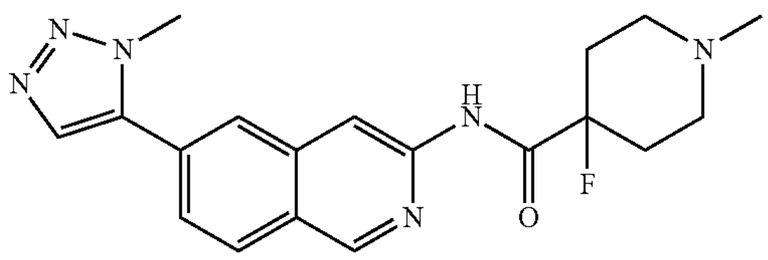
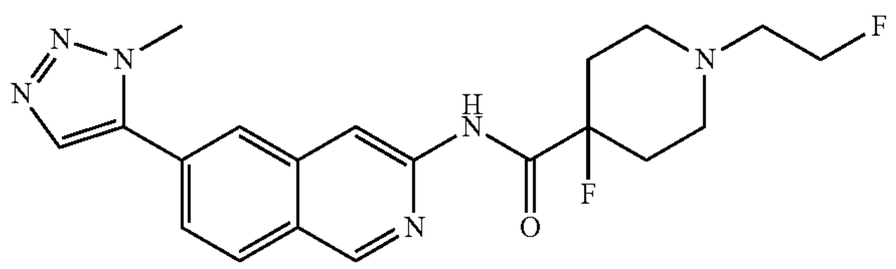
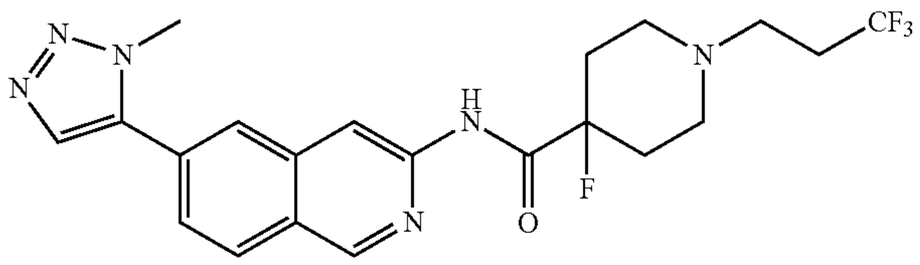
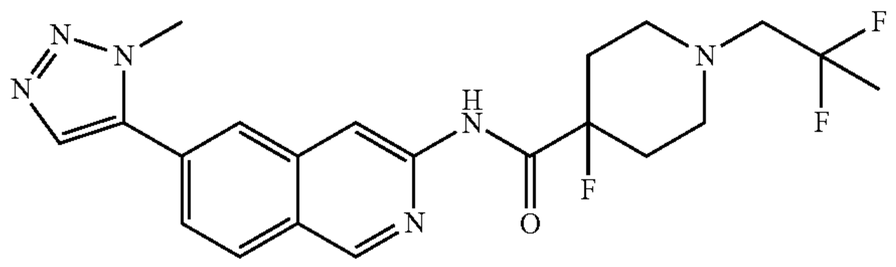
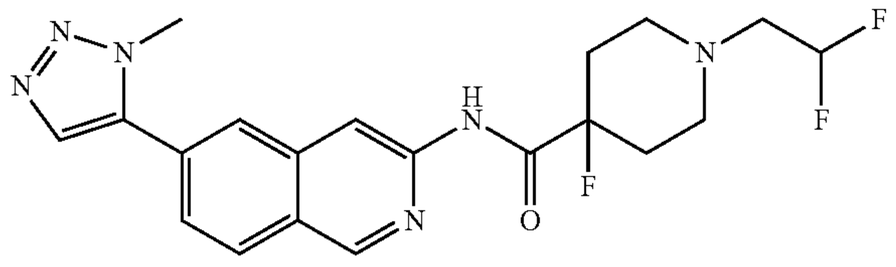
	249
	250
	251
	252
	253
	254
	255
	256
	257

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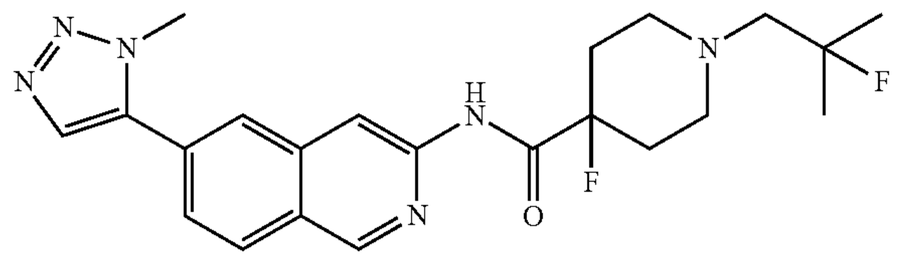
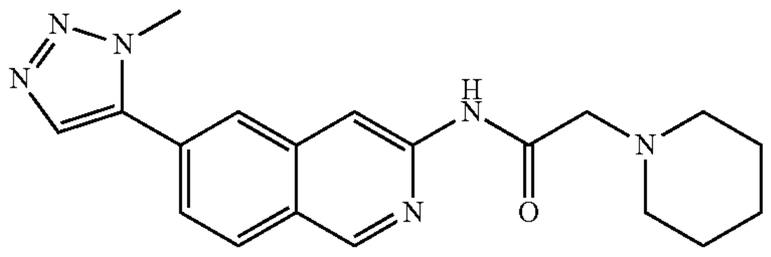
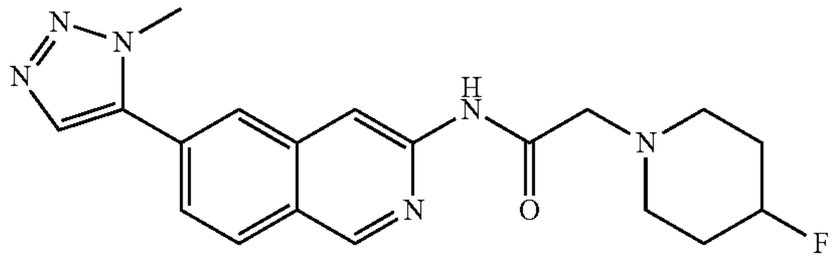
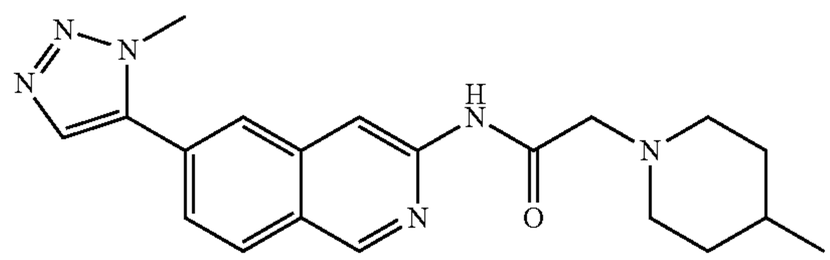
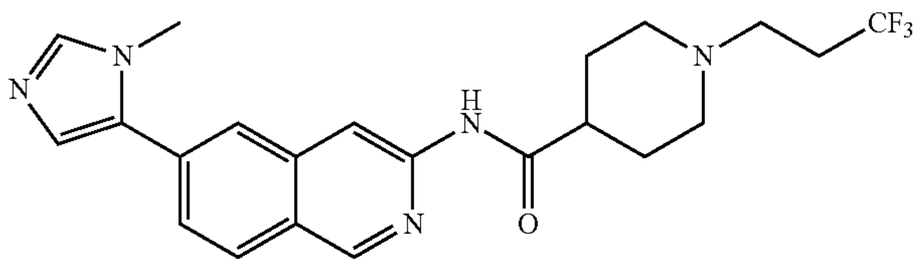
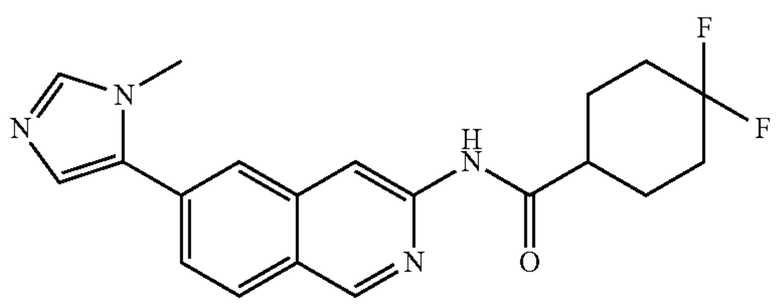
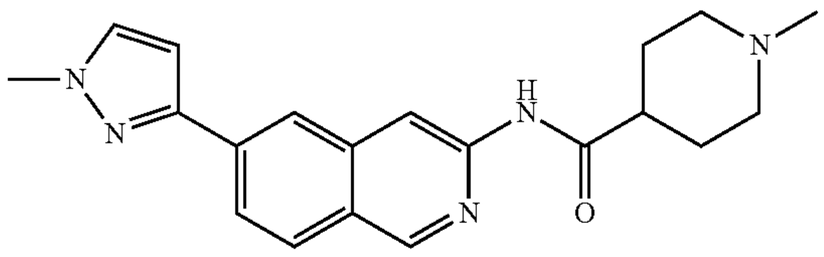
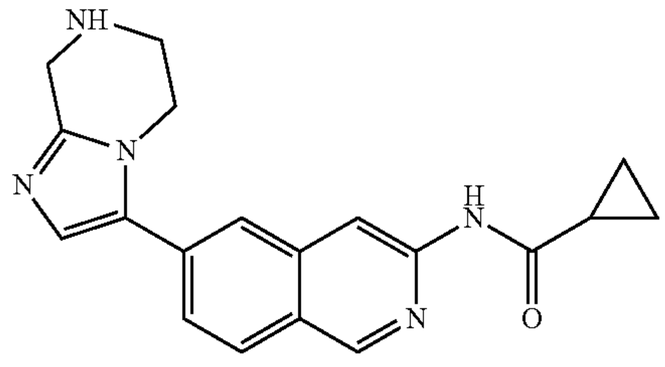
	258
	259
	260
	261
	262
	263
	264
	265

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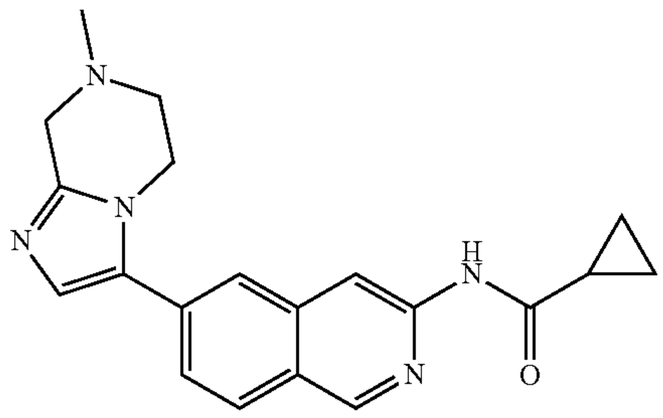
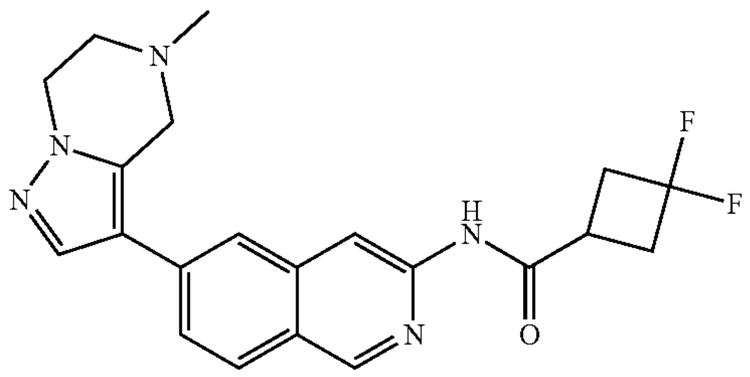
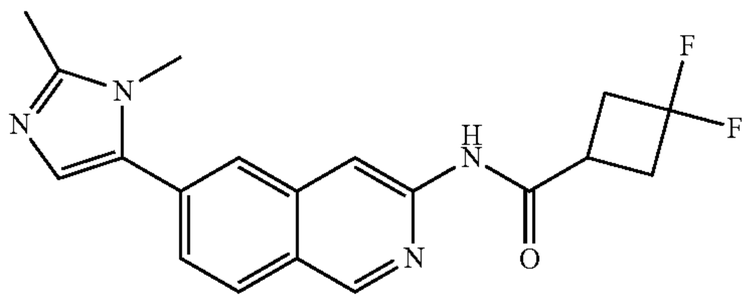
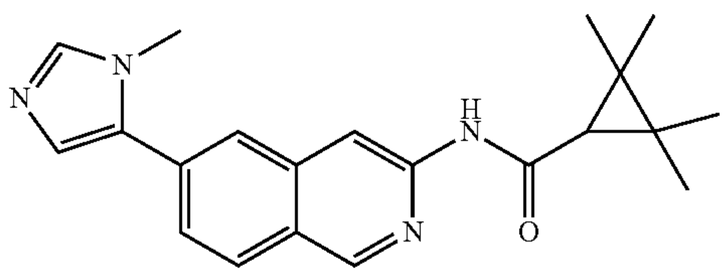
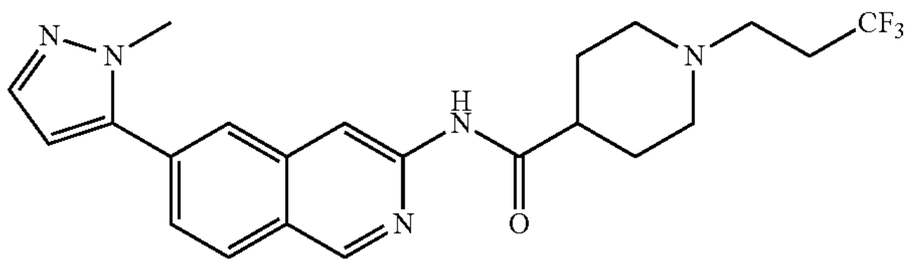
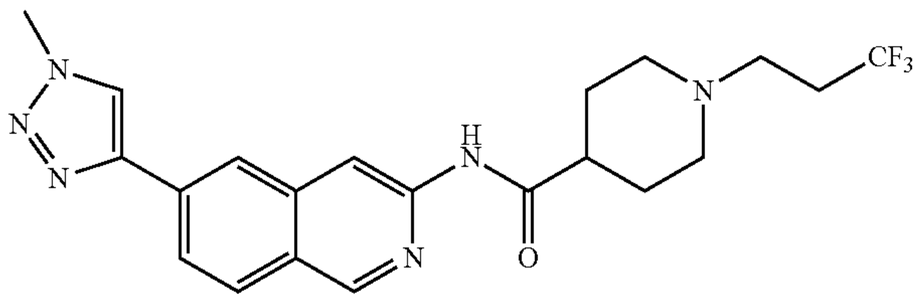
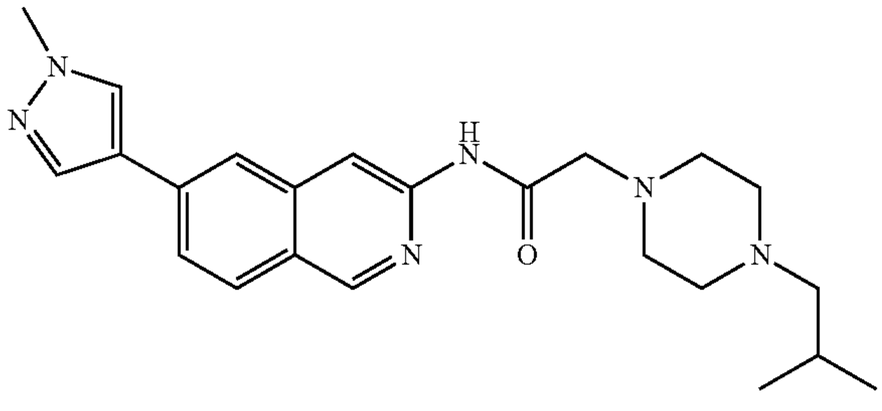
266	
267	
268	
269	
270	
271	
272	

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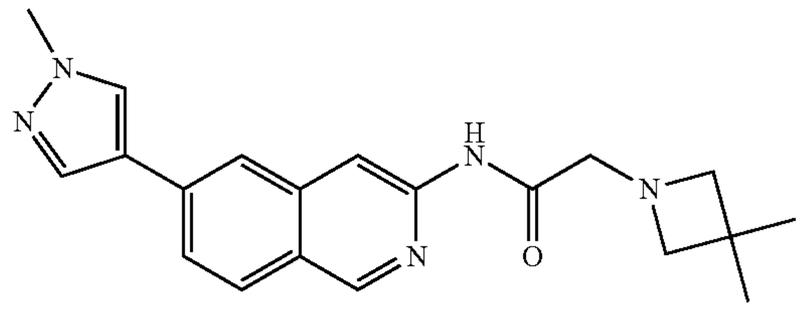
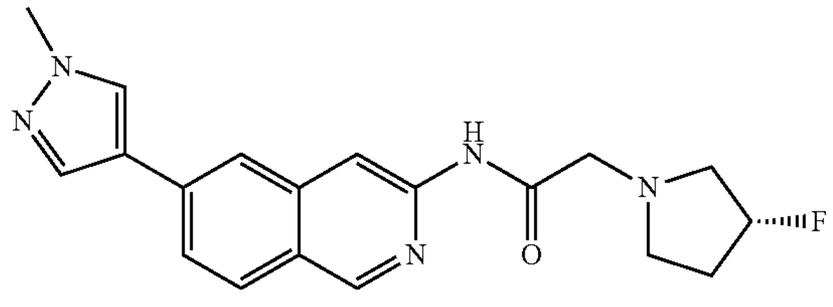
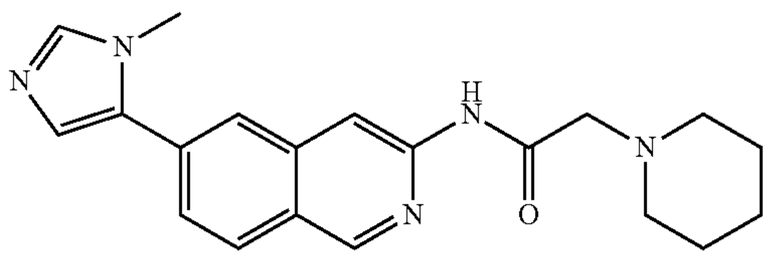
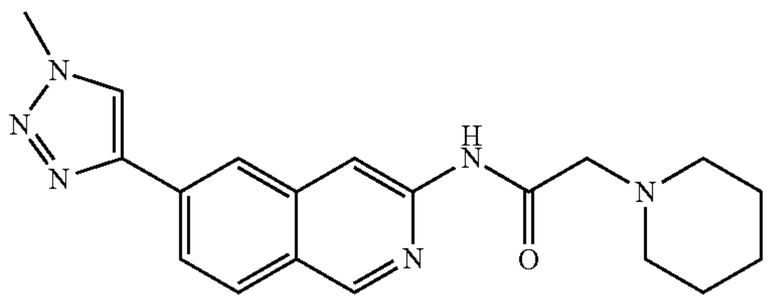
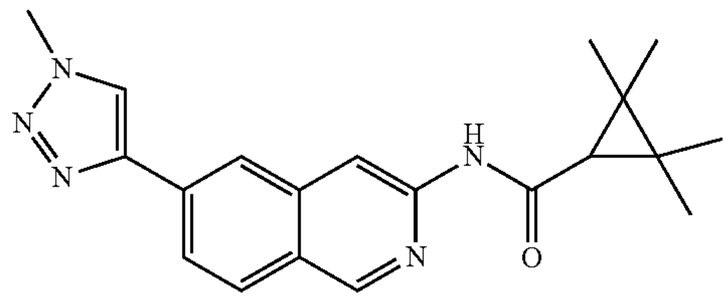
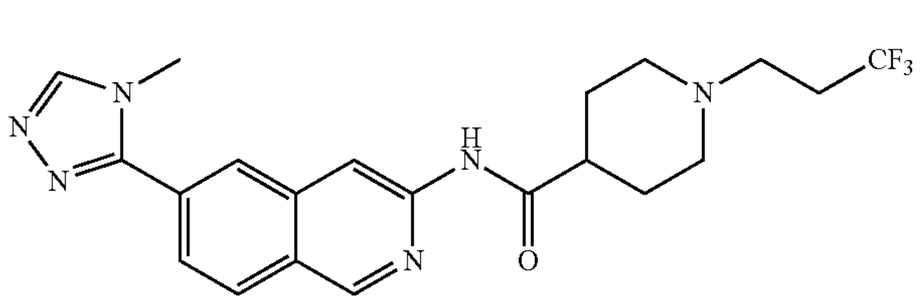
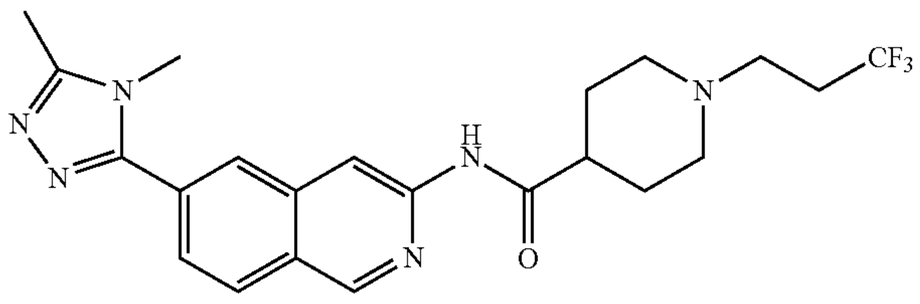
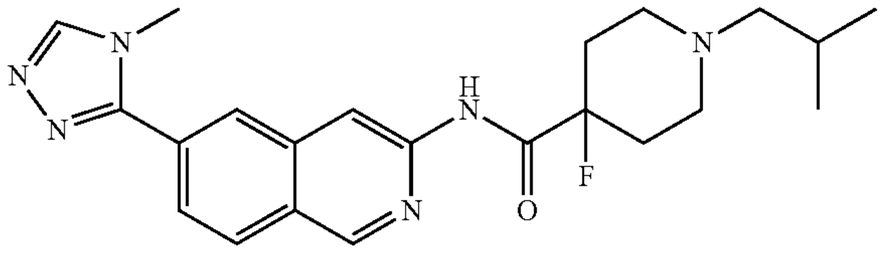
273	
274	
275	
276	
277	
278	
279	
280	

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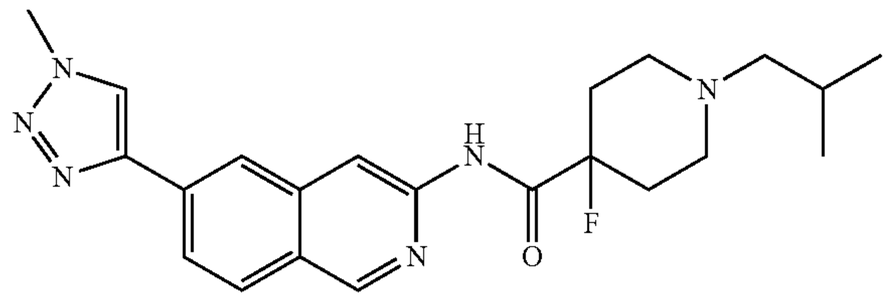
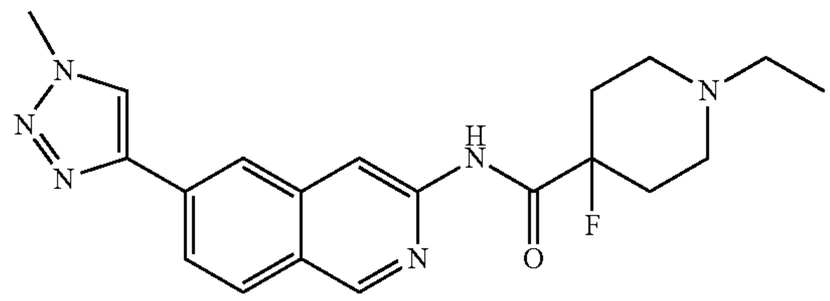
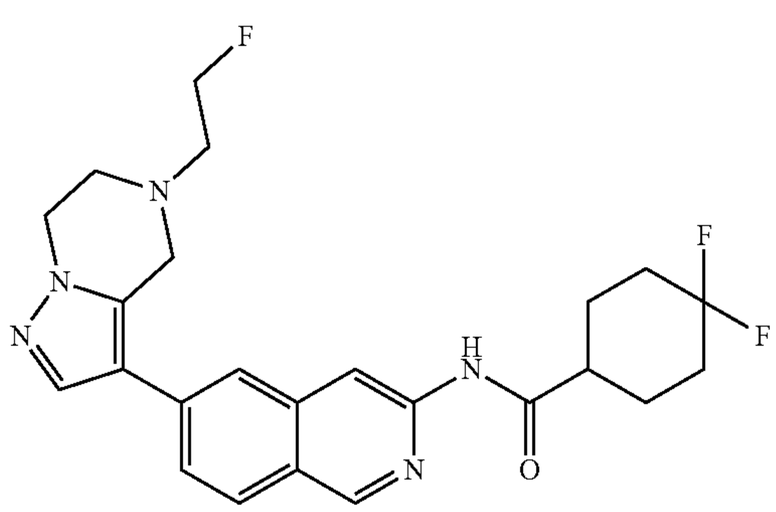
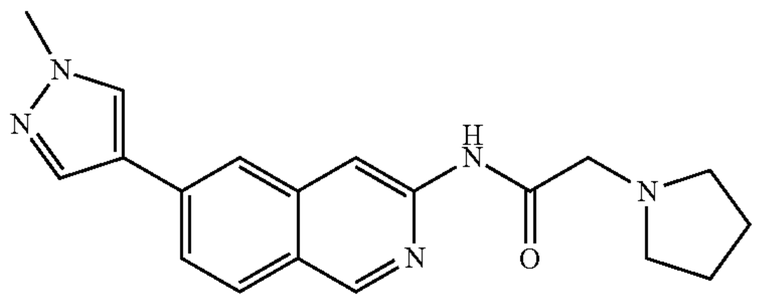
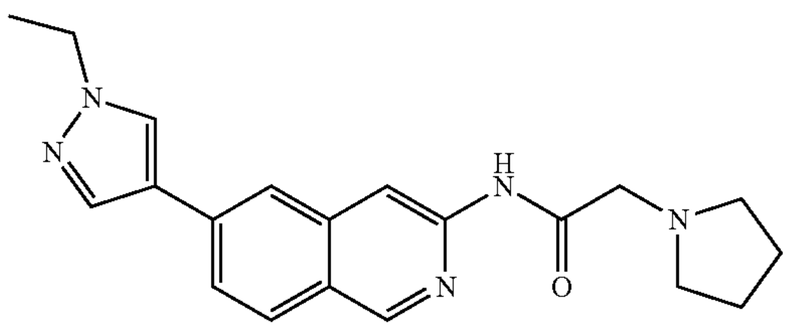
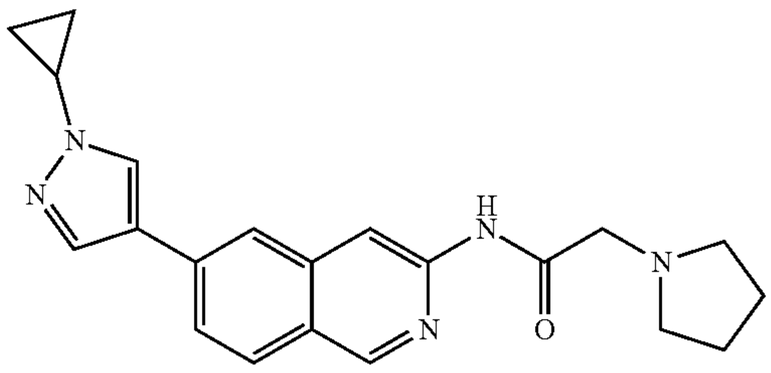
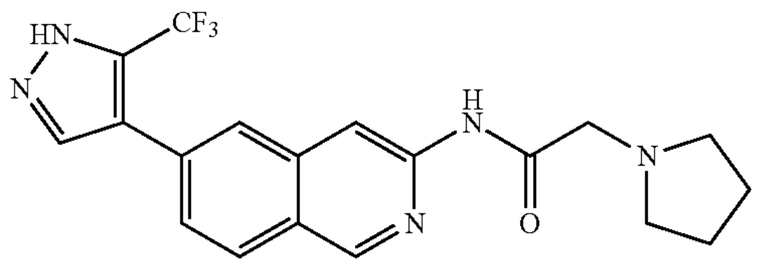
	281
	282
	283
	284
	285
	286
	287

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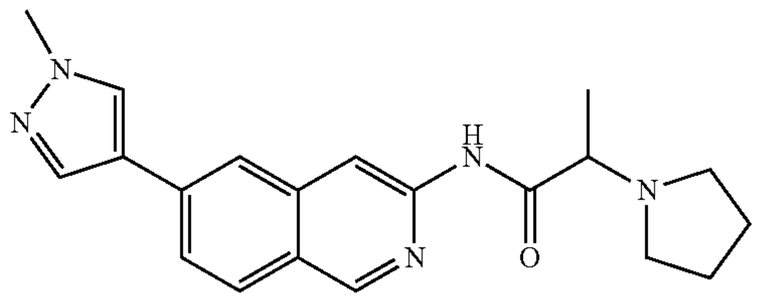
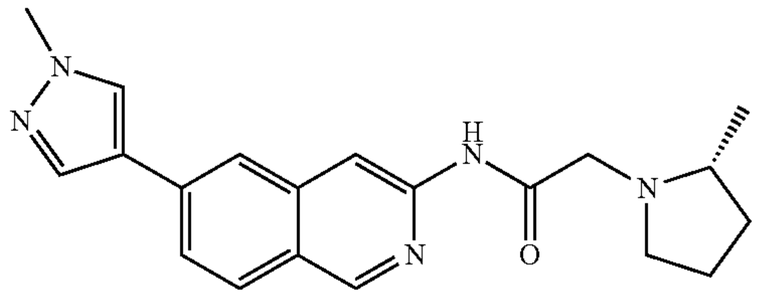
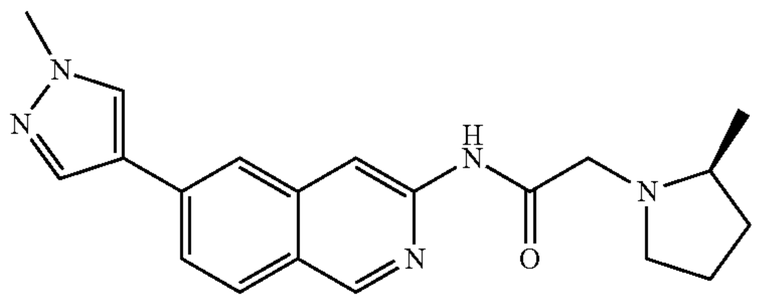
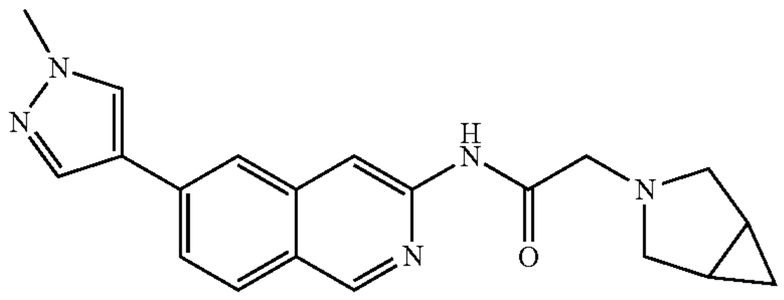
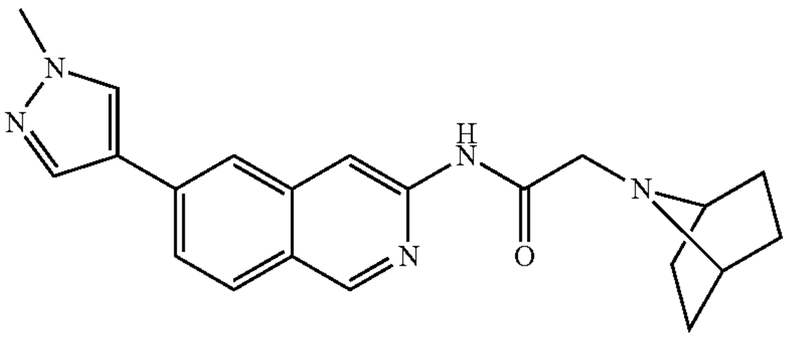
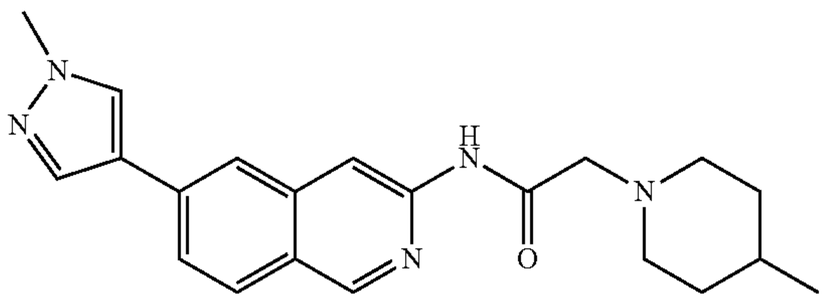
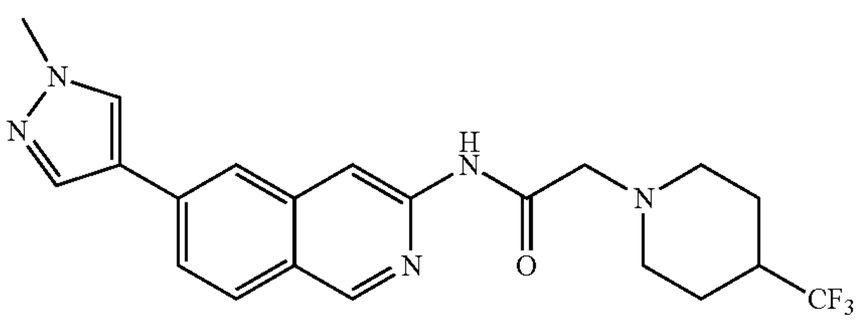
288	
289	
290	
291	
292	
293	
294	

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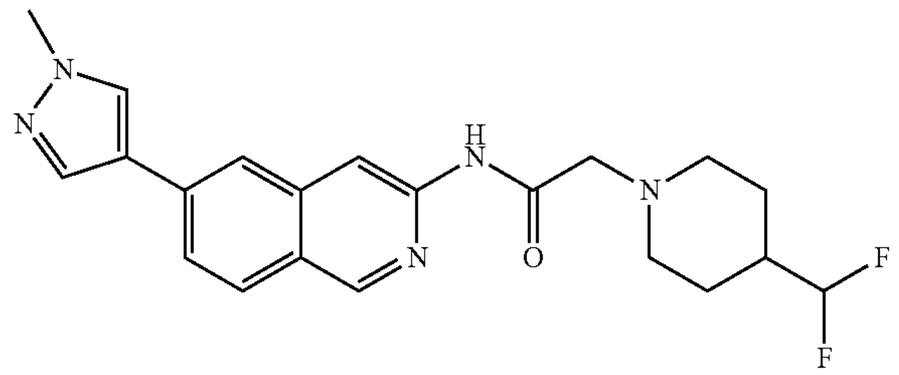
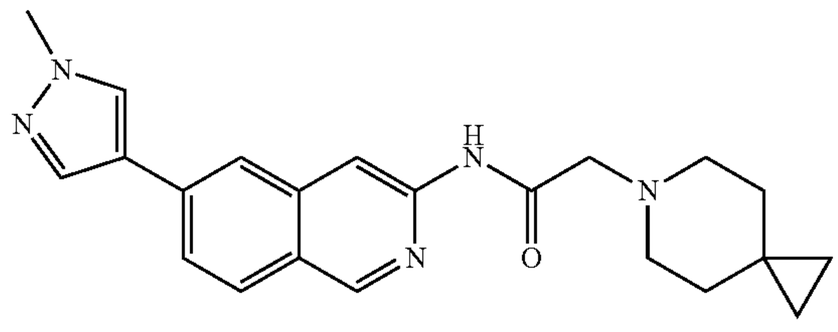
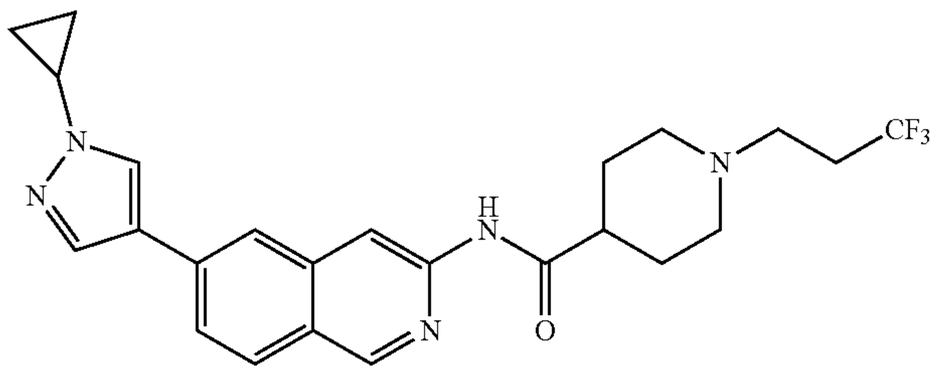
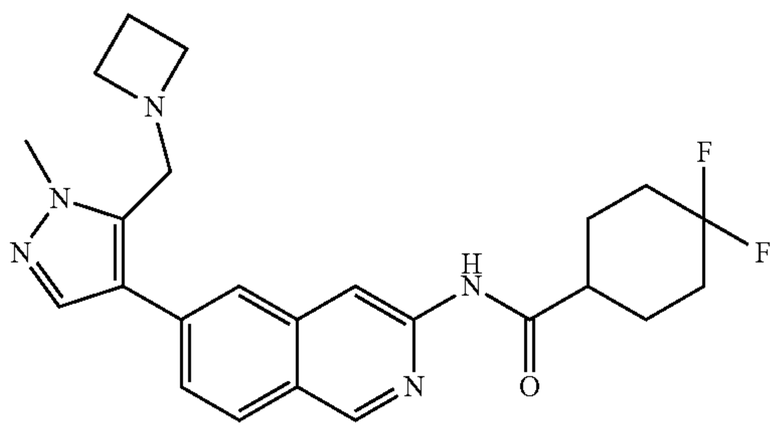
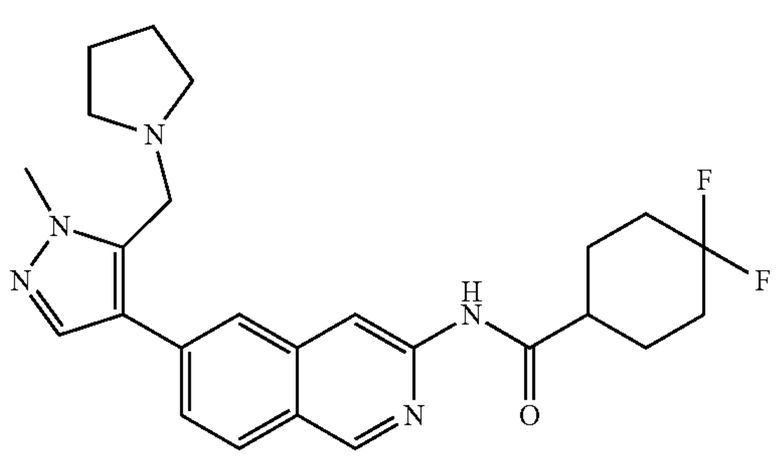
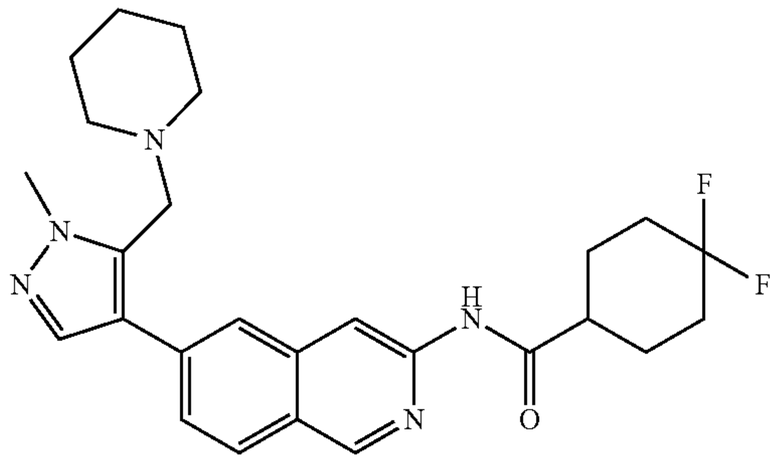
295	
296	
297	
298	
299	
300	

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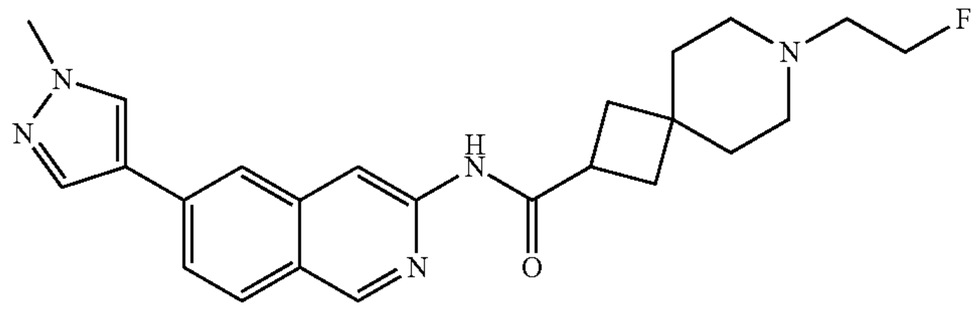

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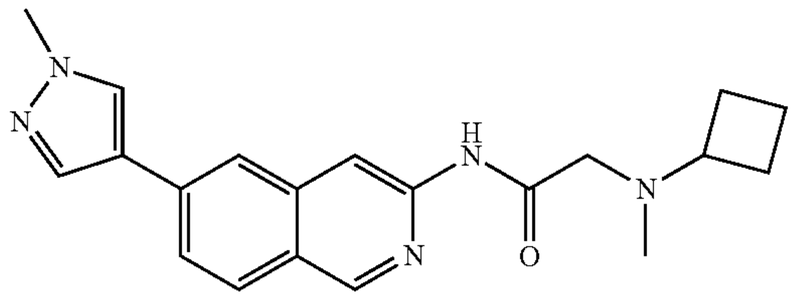

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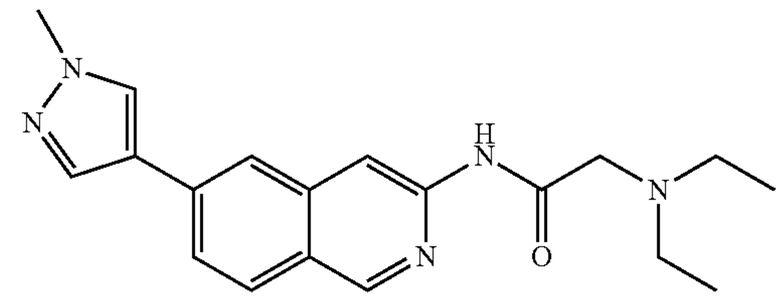

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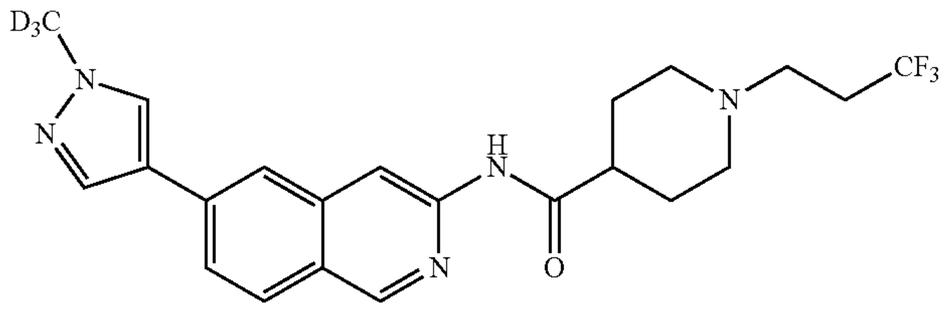

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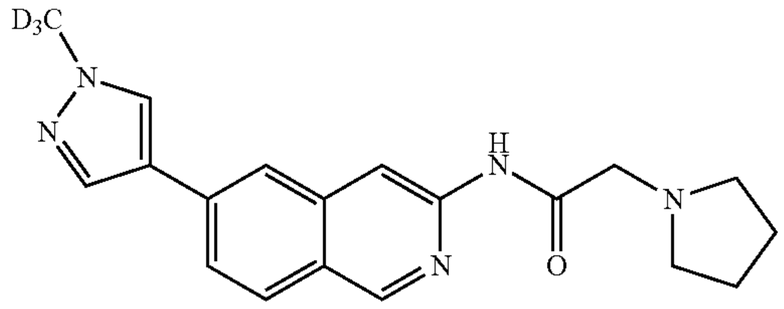

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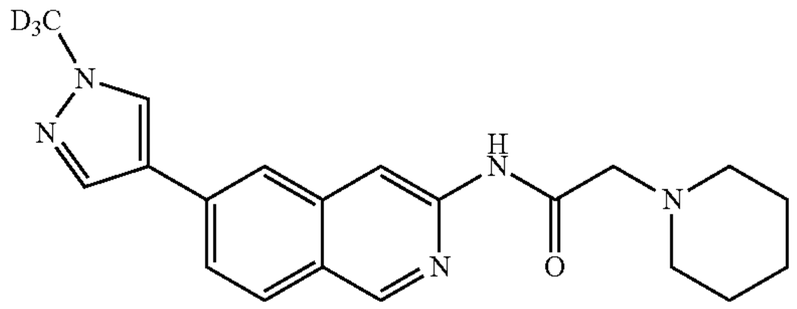

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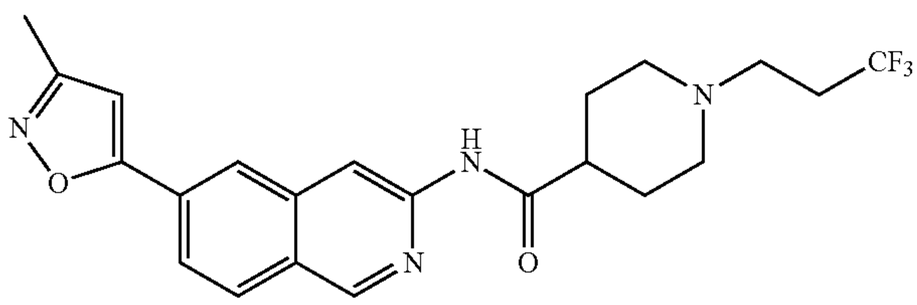

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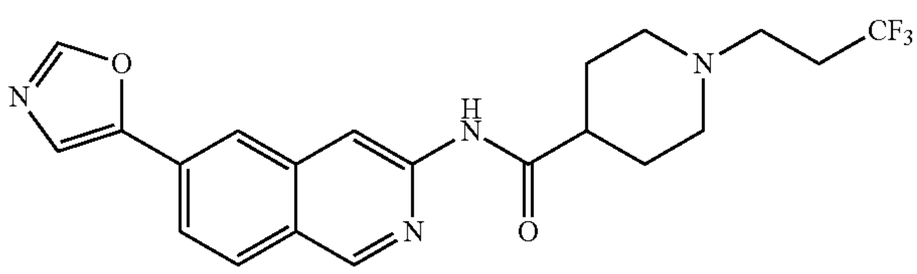

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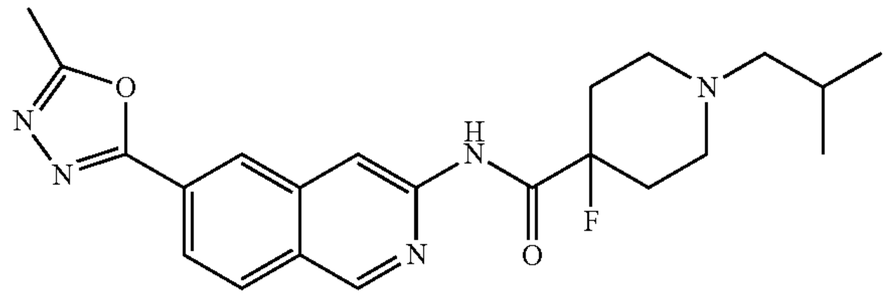

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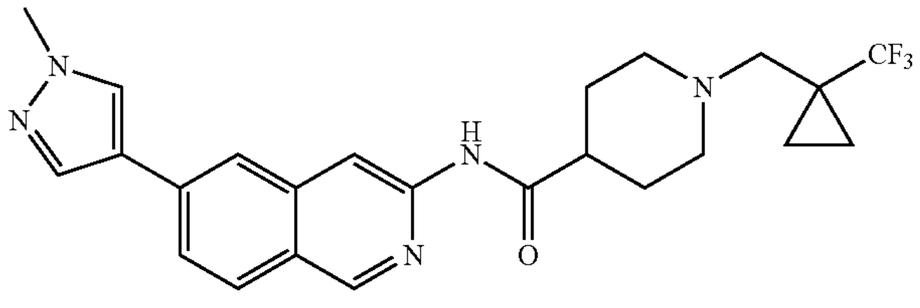

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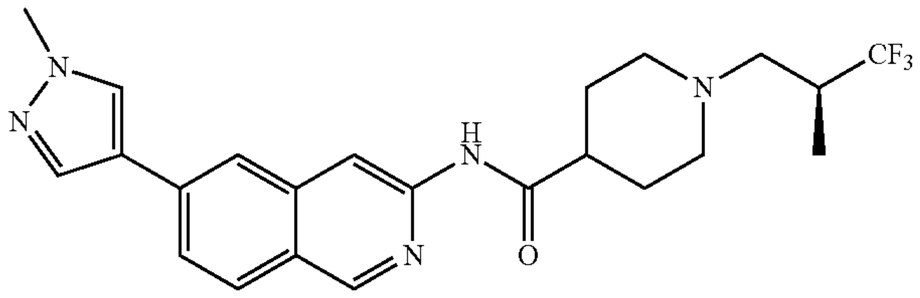

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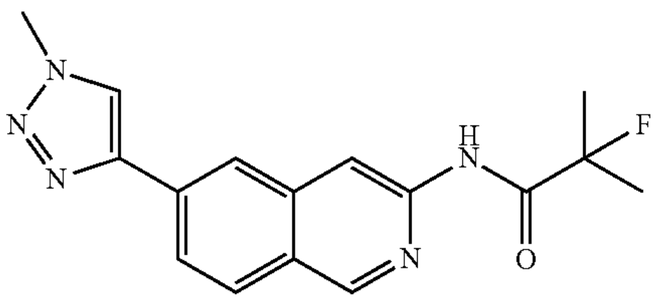

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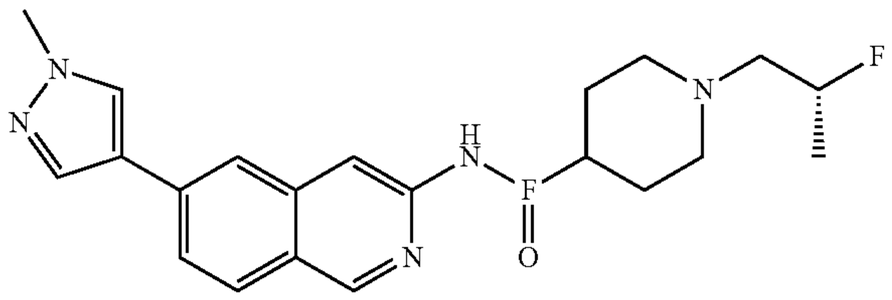

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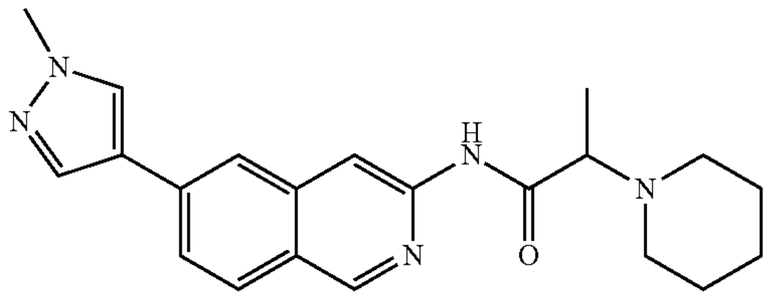

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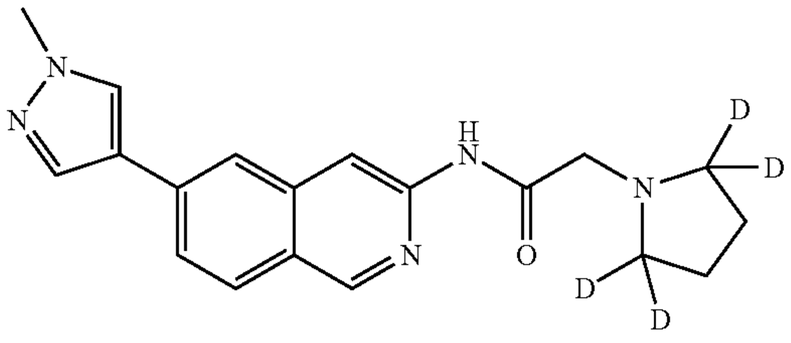

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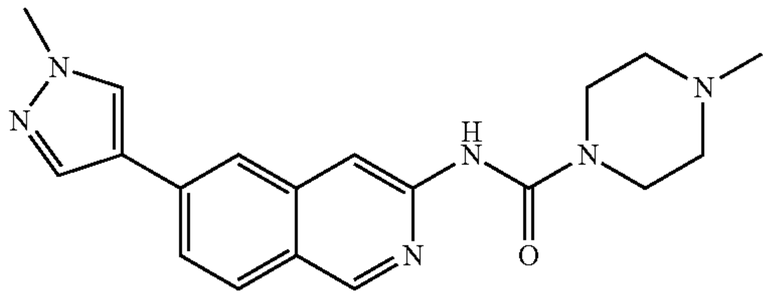

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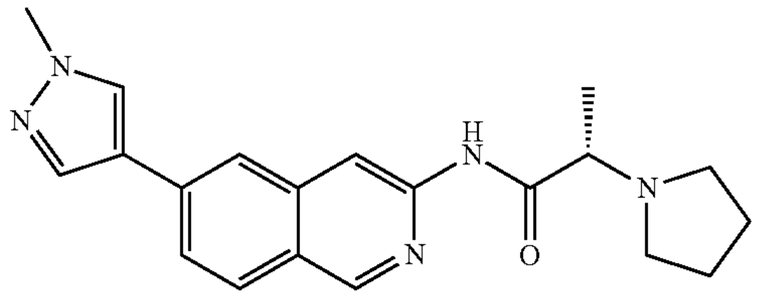
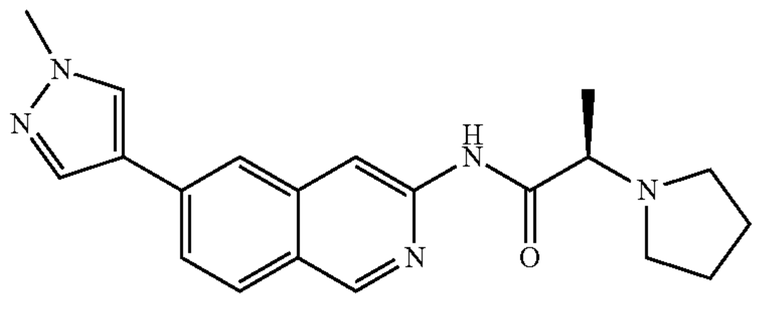
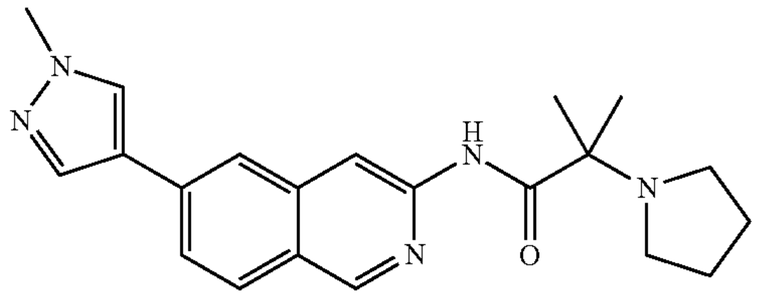
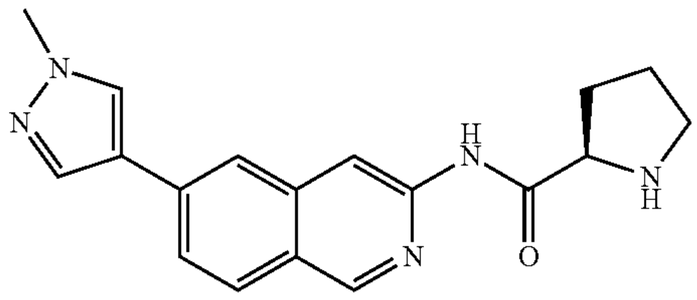
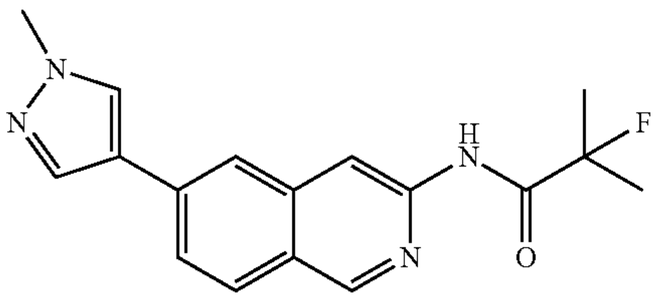
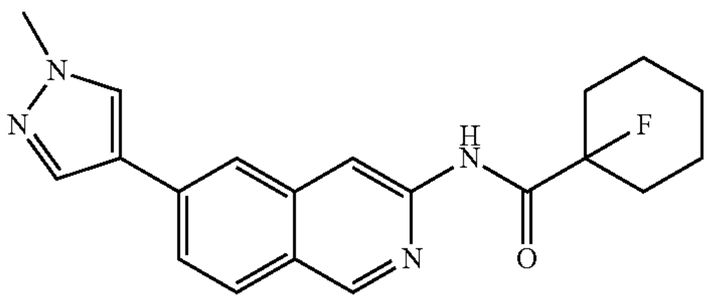
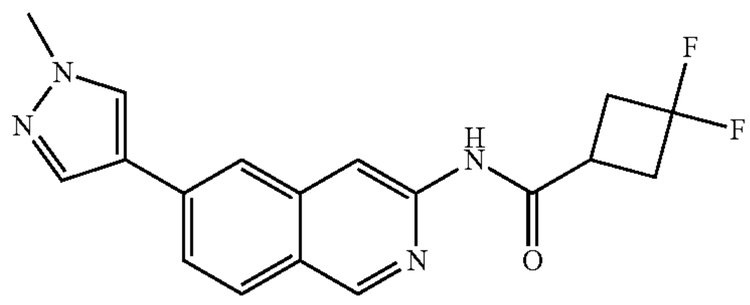
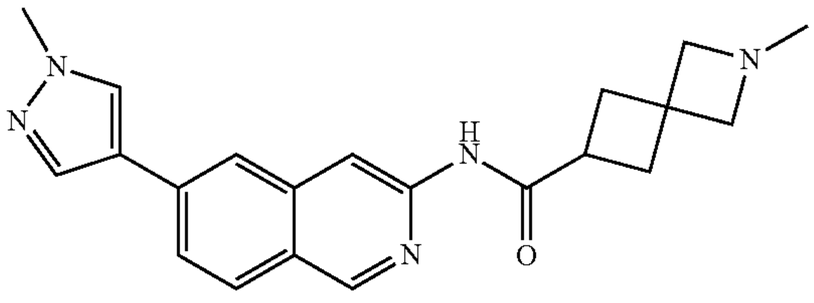
317	
318	
319	
320	
321	
322	
323	
324	

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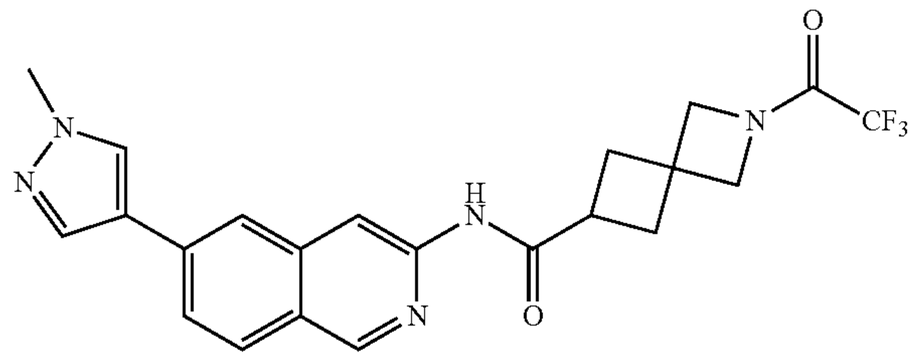
325	
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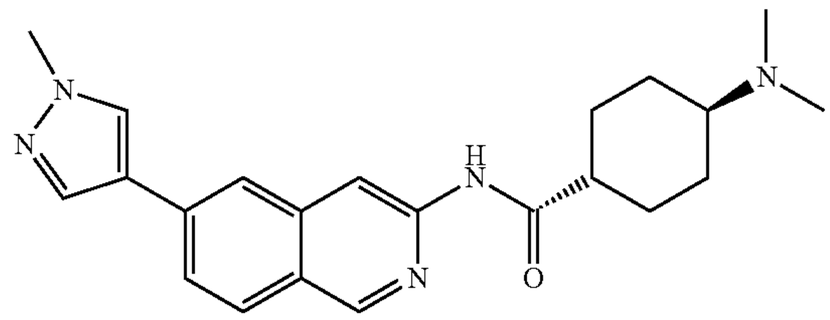
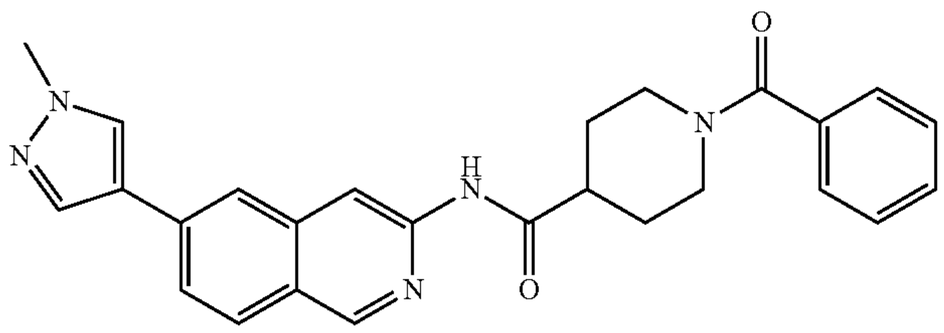
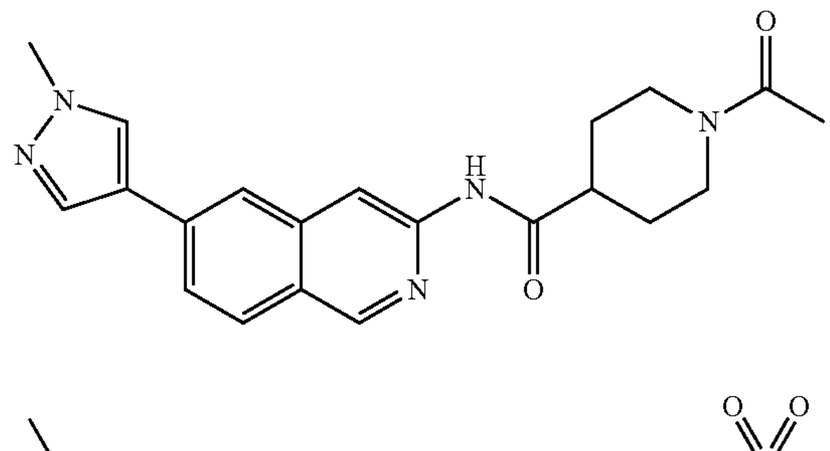
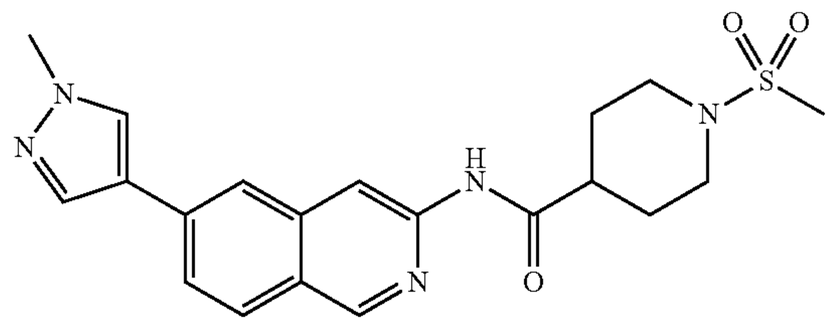
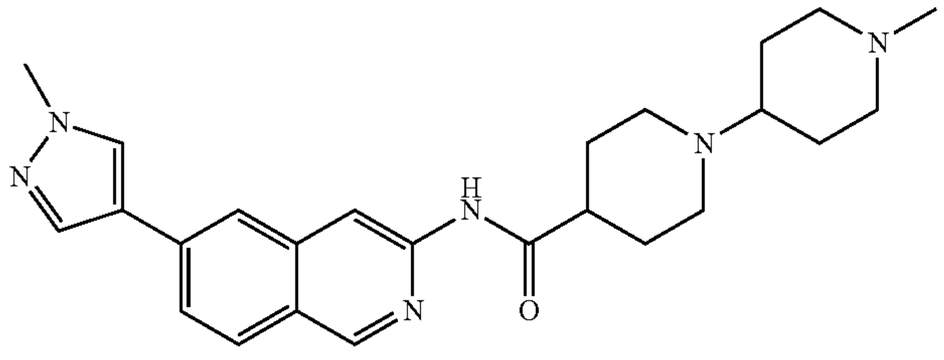
327	
328	
329	
330	
331	

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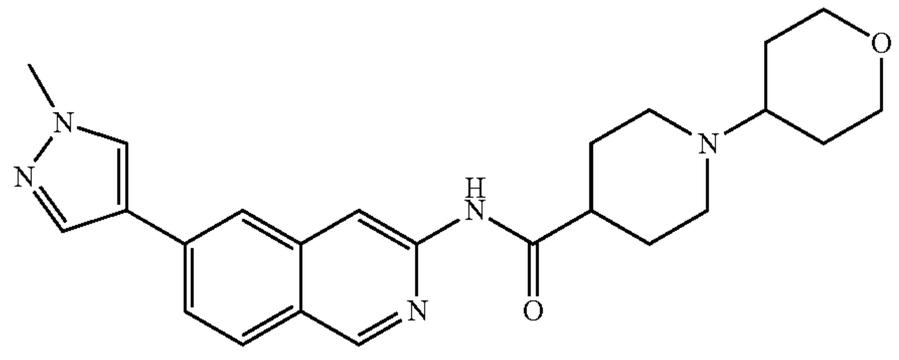
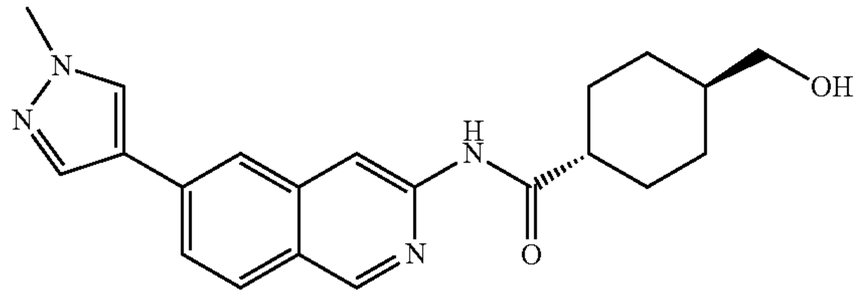
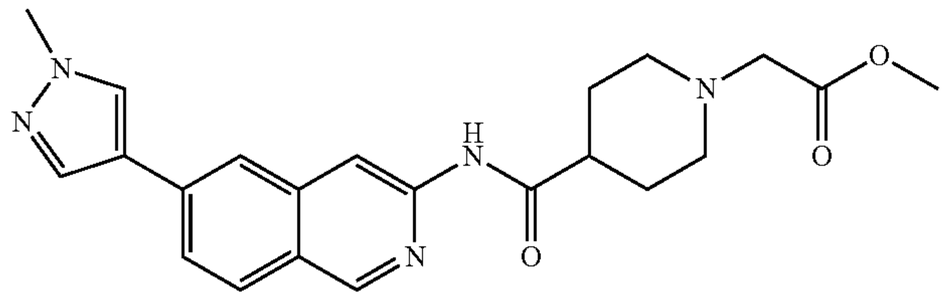
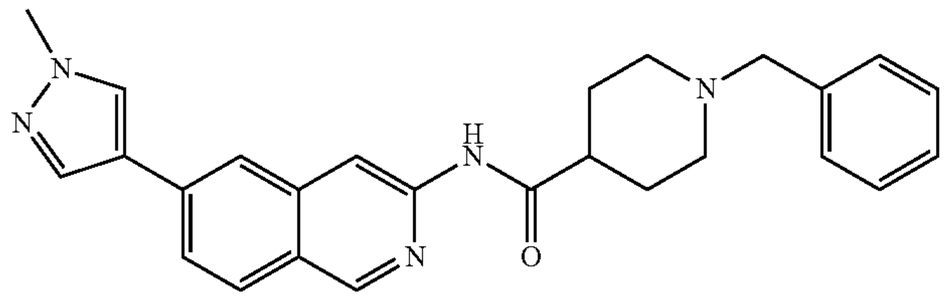
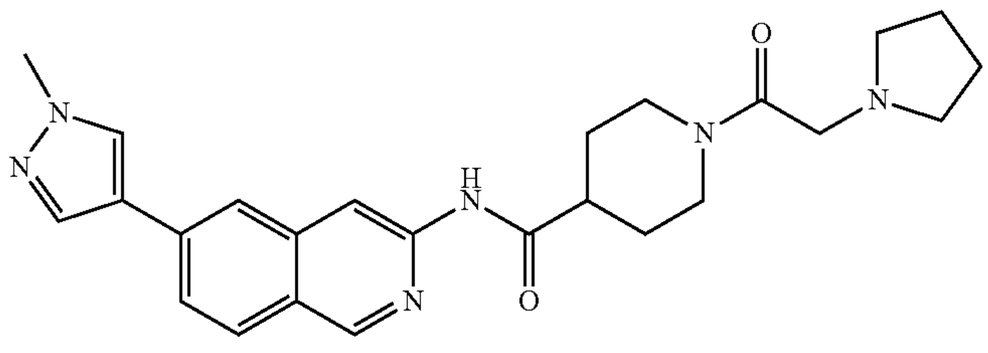
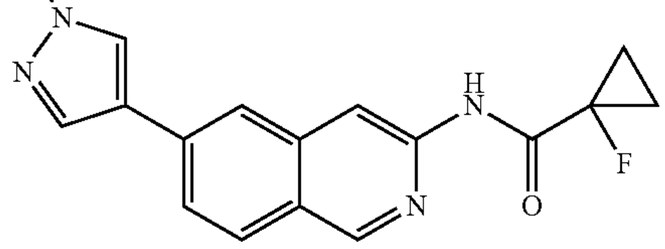
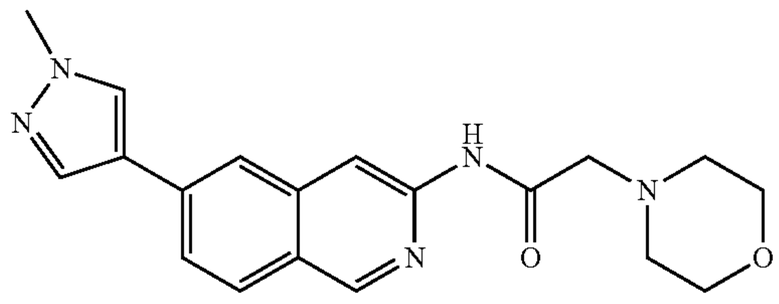
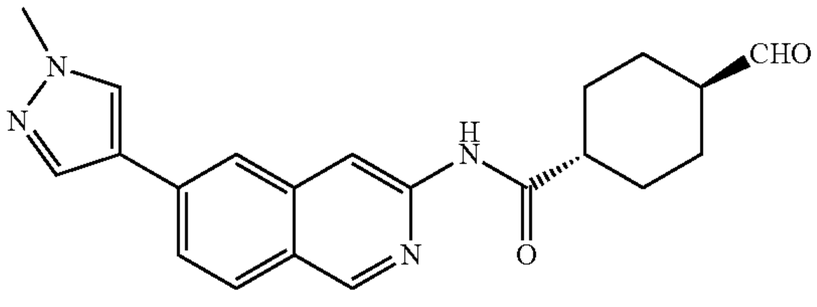
332	
333	
334	
335	
336	
337	
338	
339	

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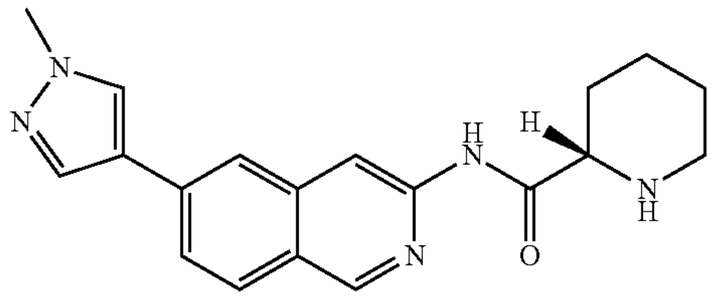

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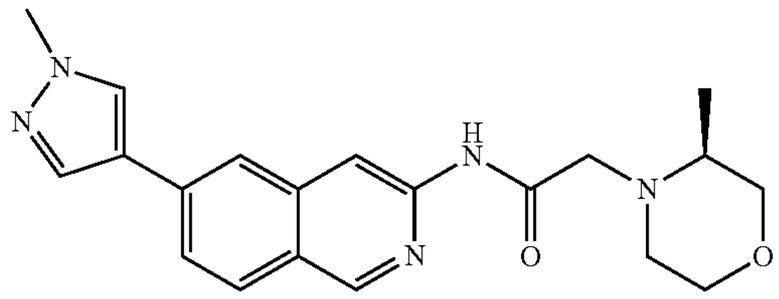

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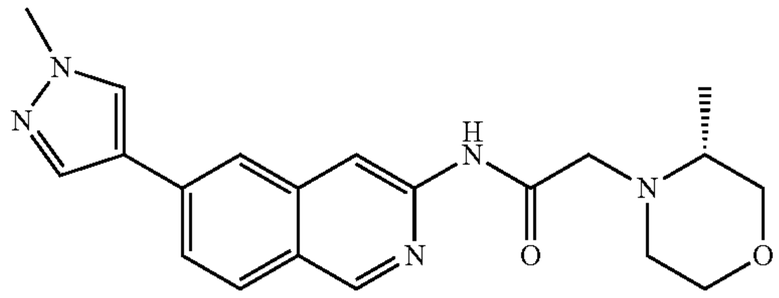

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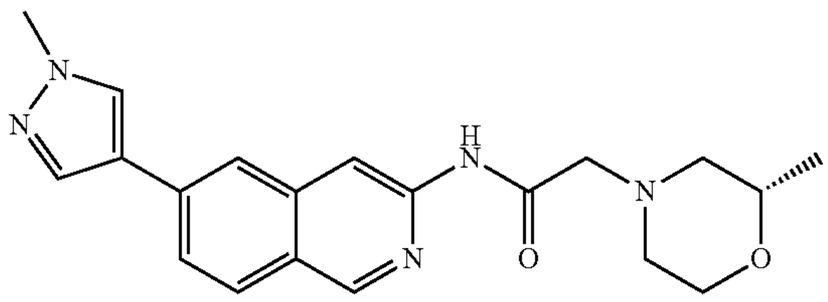

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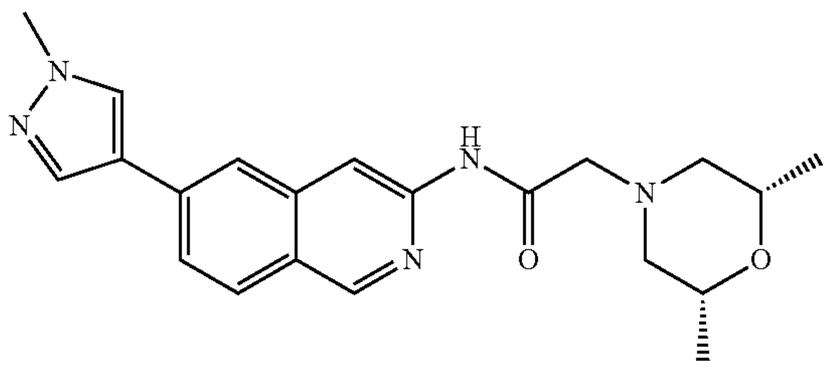

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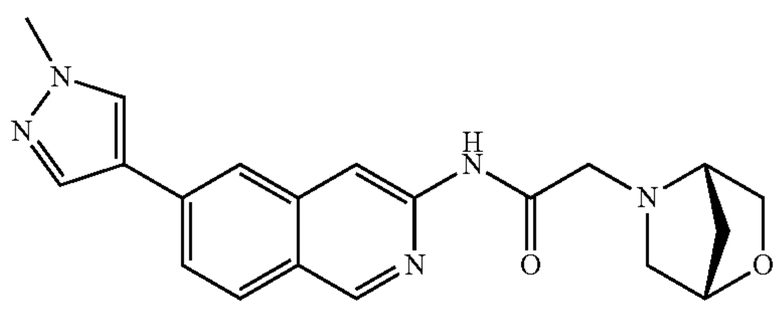

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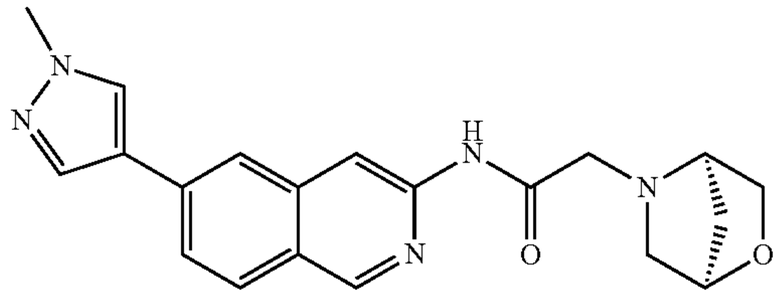

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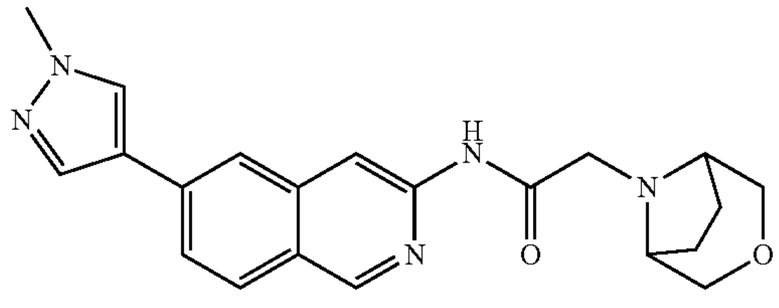

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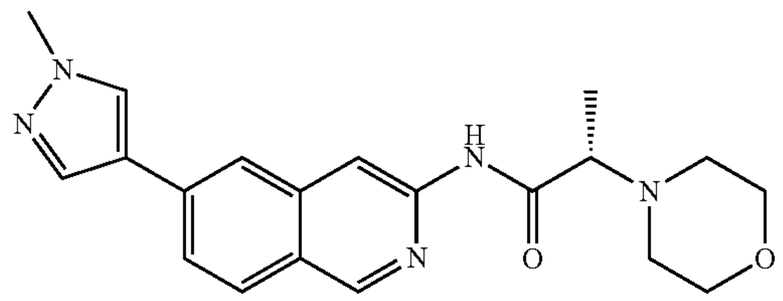

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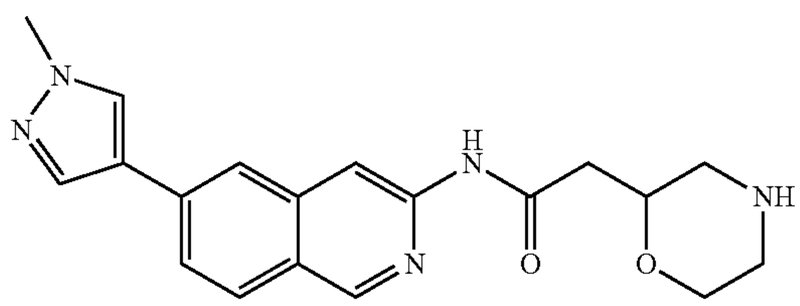

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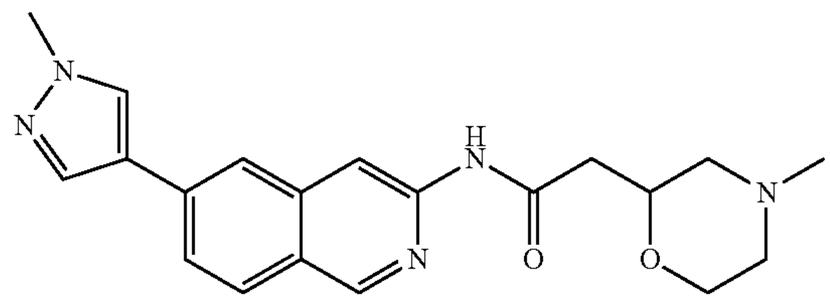

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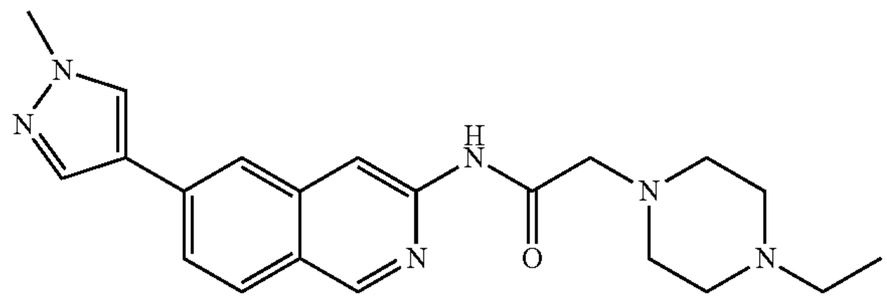

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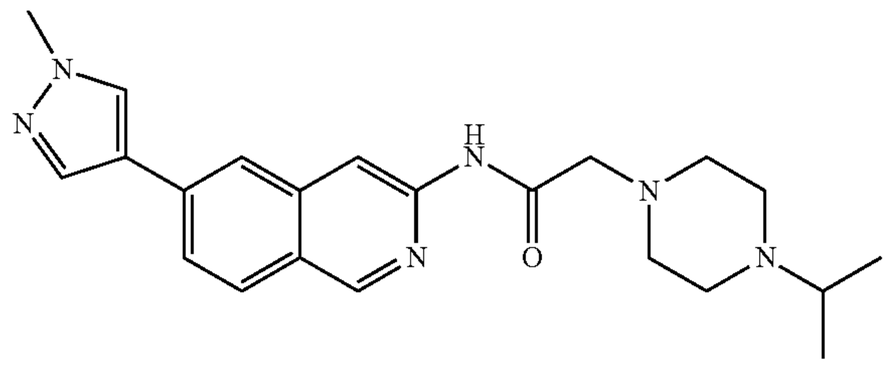

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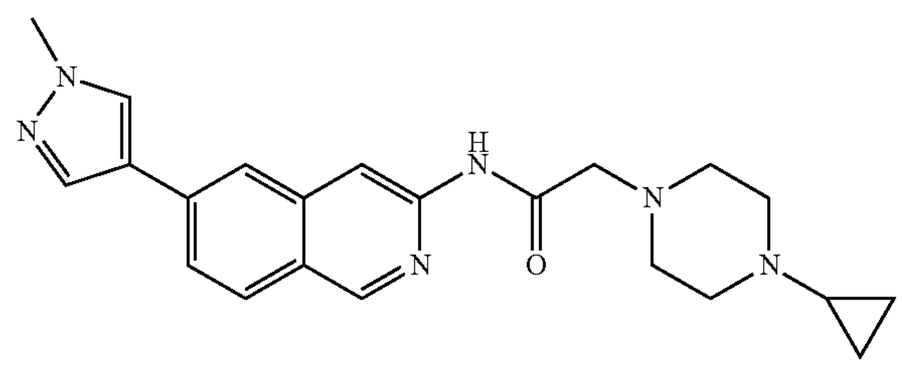

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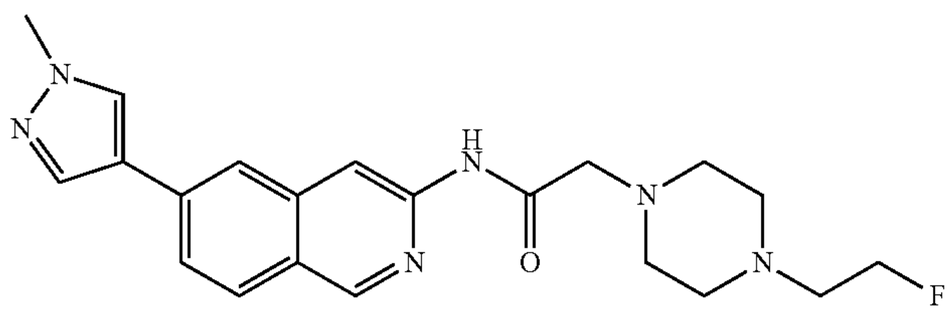

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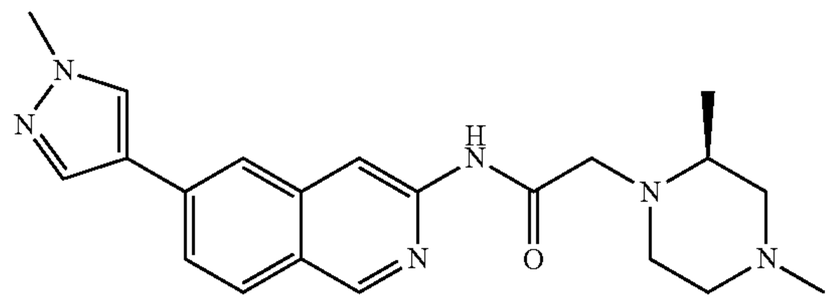
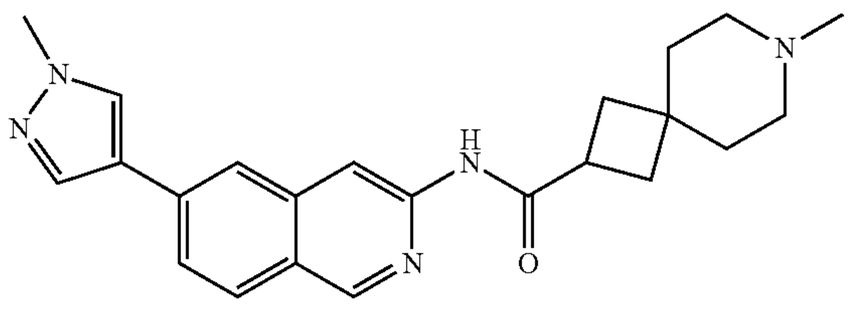
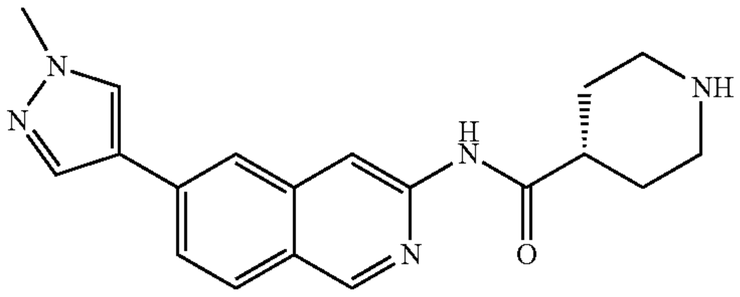
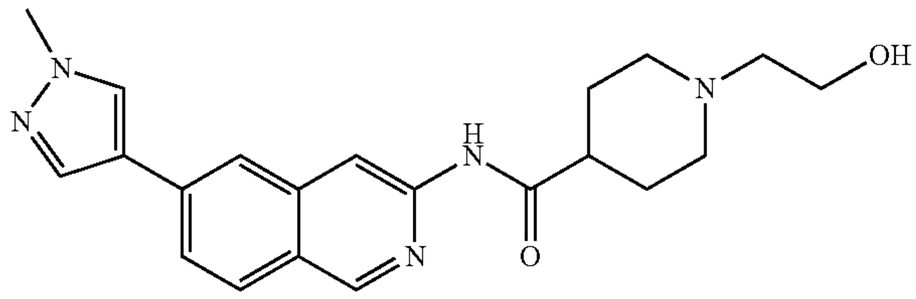
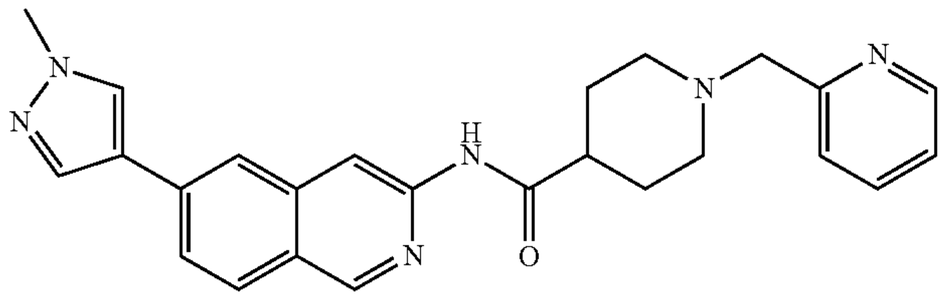
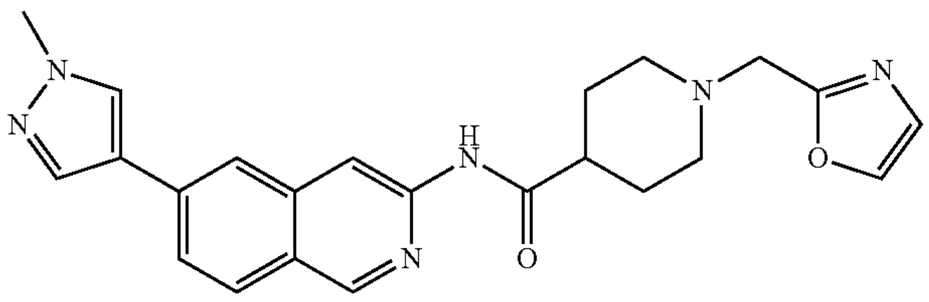
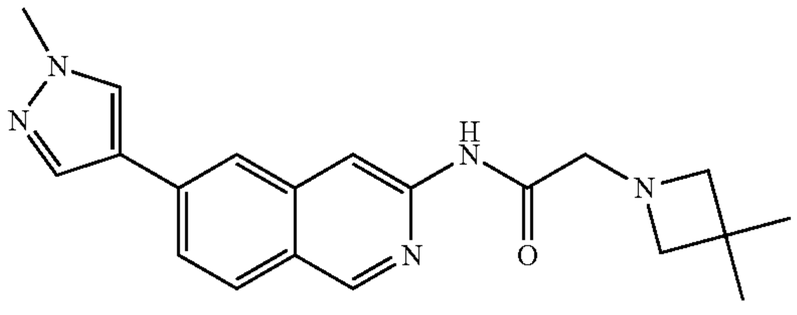
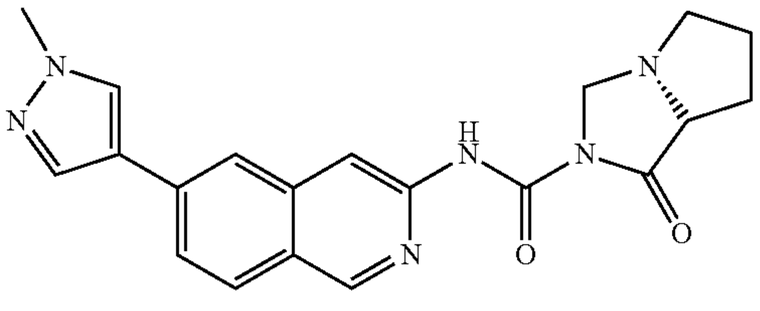
355	
356	
357	
358	
359	
360	
361	
362	

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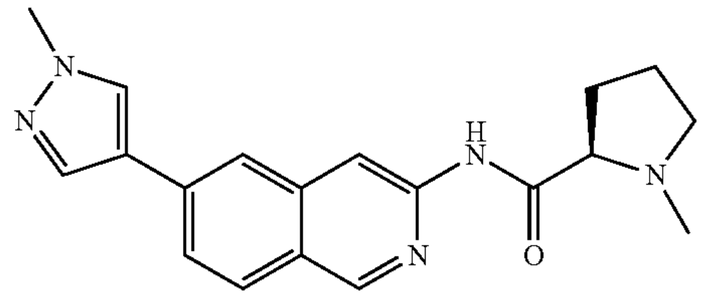
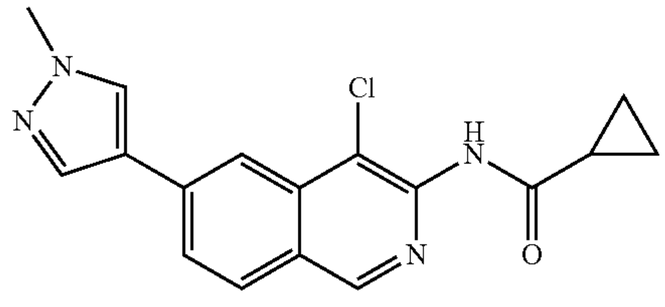
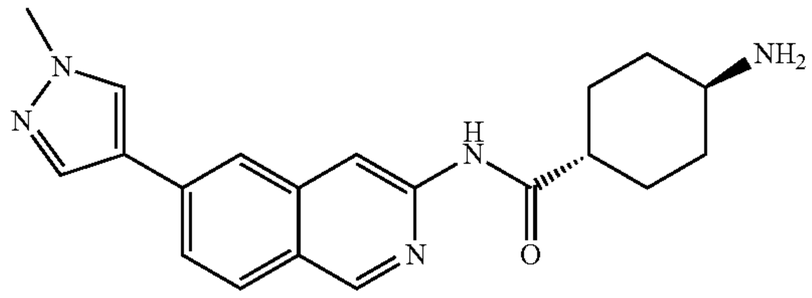
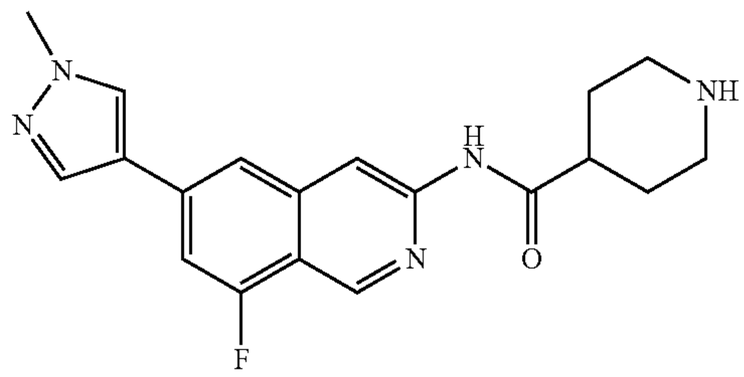
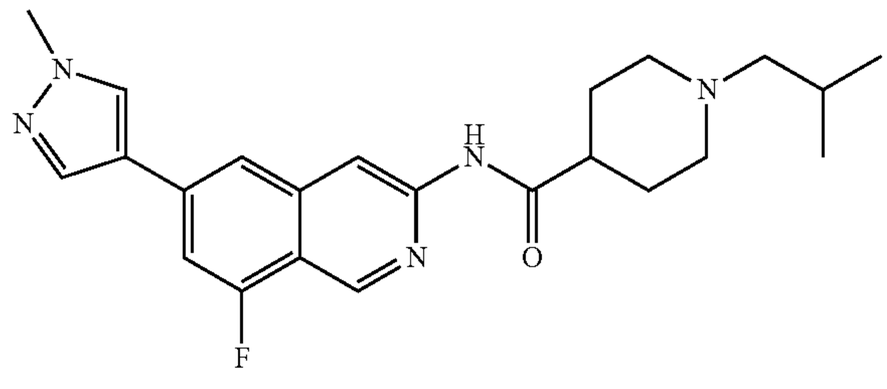
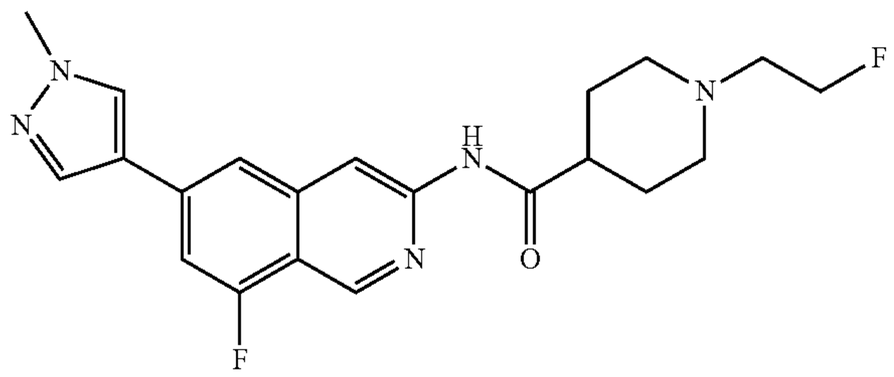
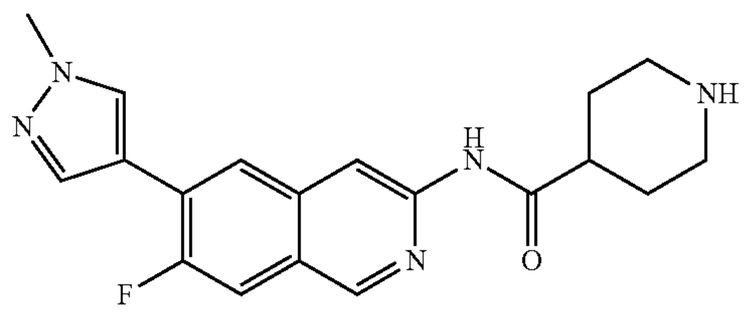
363	
364	
365	
366	
367	
368	
369	

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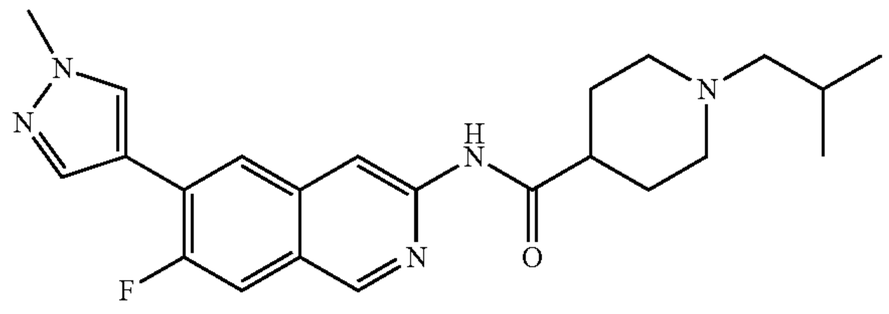
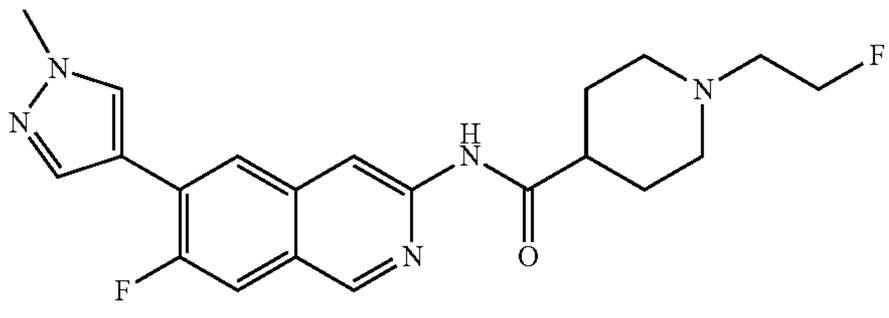
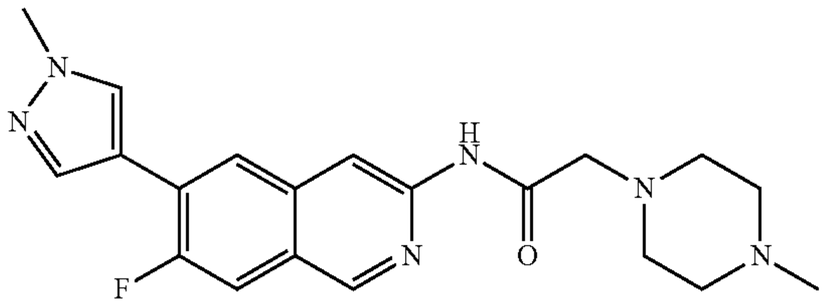
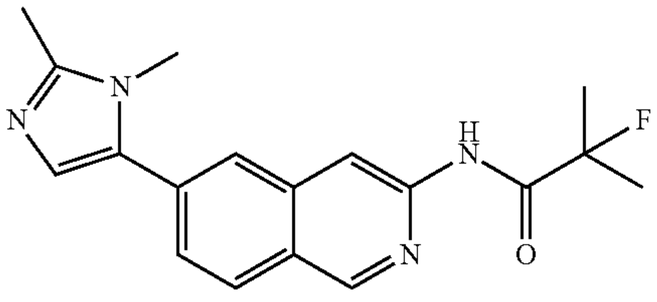
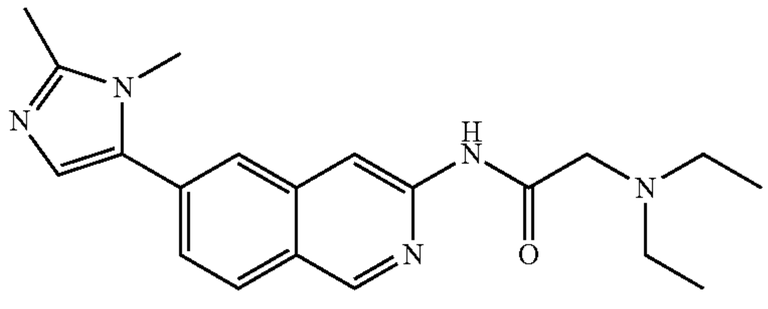
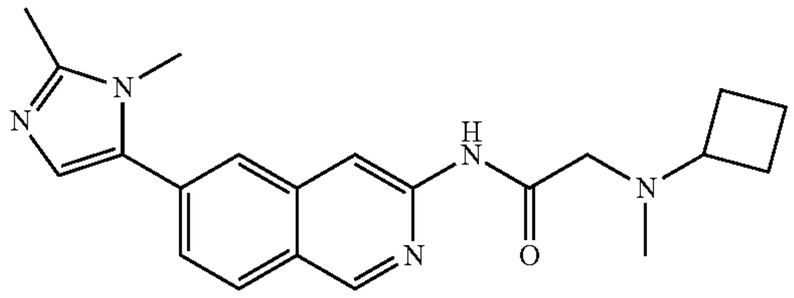
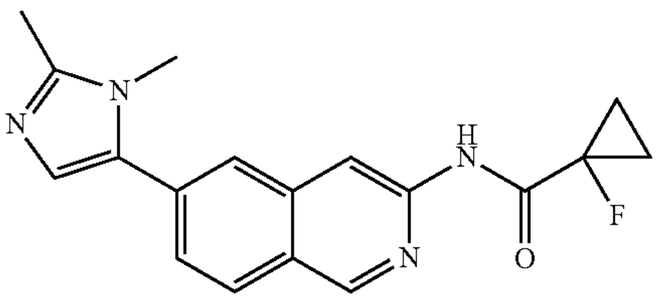
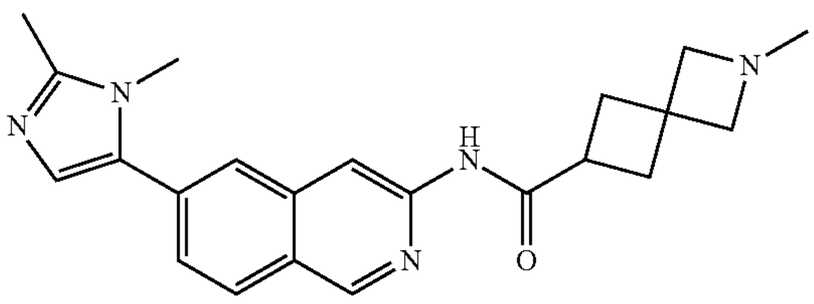
370	
371	
372	
373	
374	
375	
376	
377	

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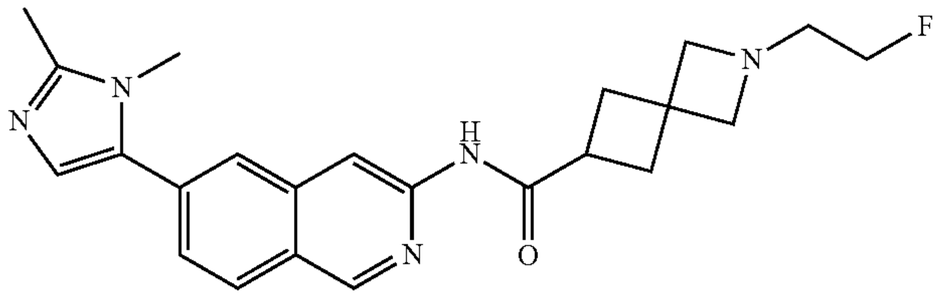
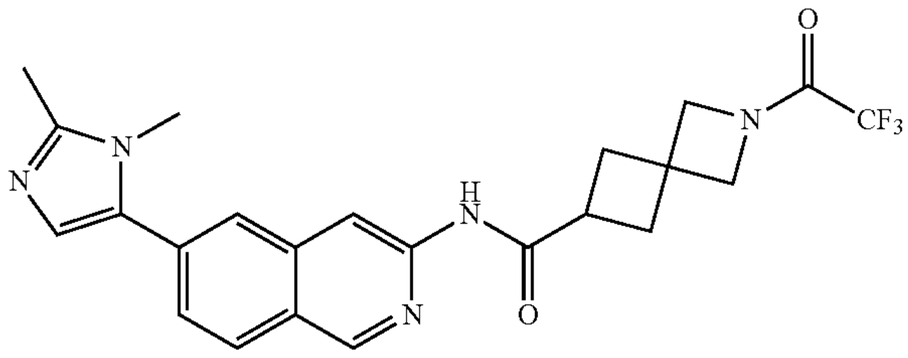
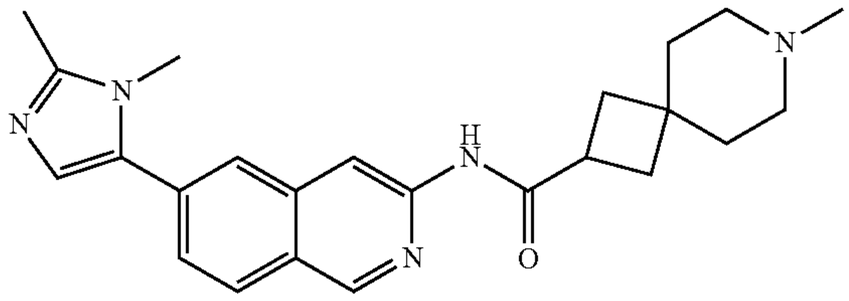
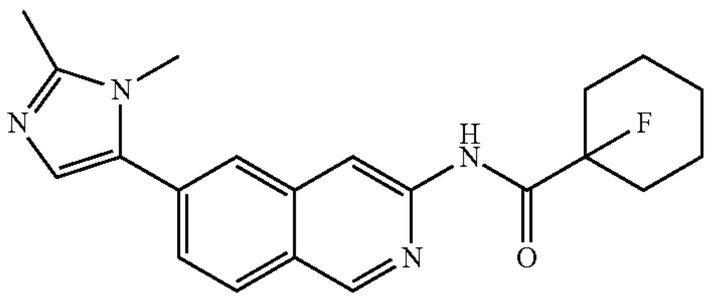
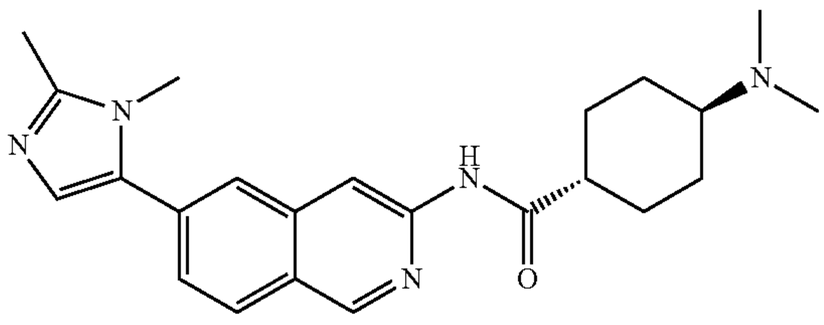
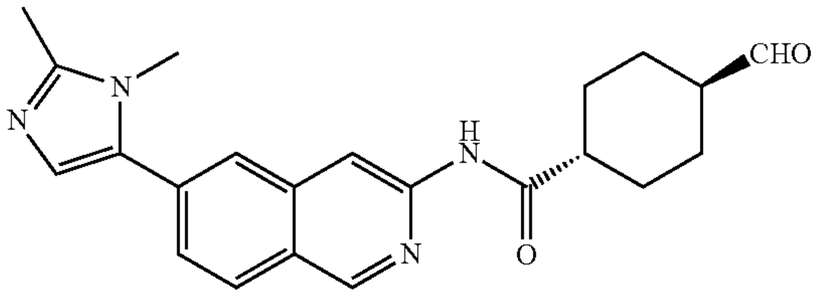
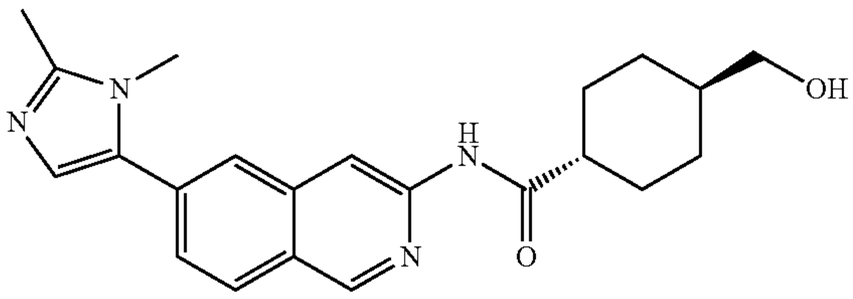
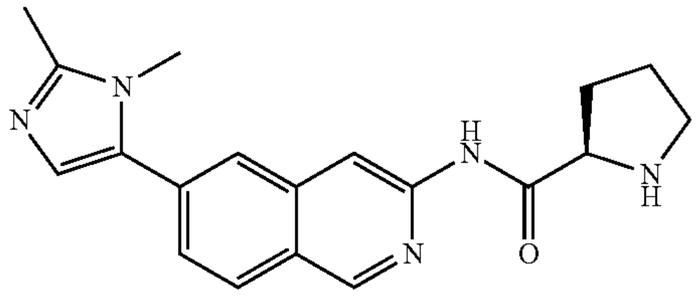
	378
	379
	380
	381
	382
	383
	384
	385

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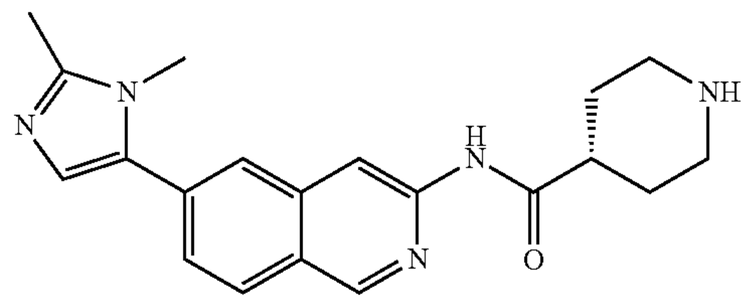

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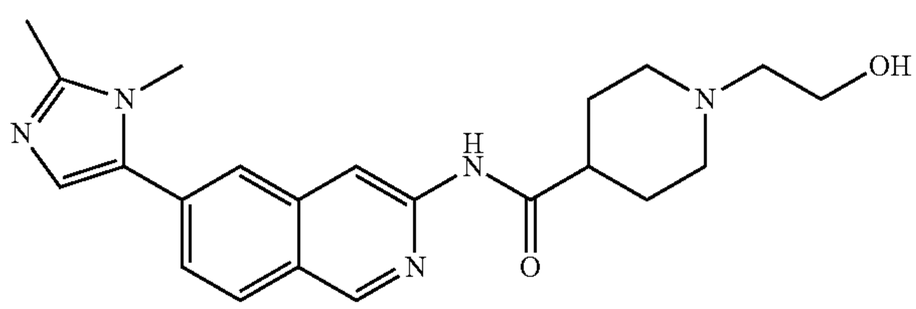

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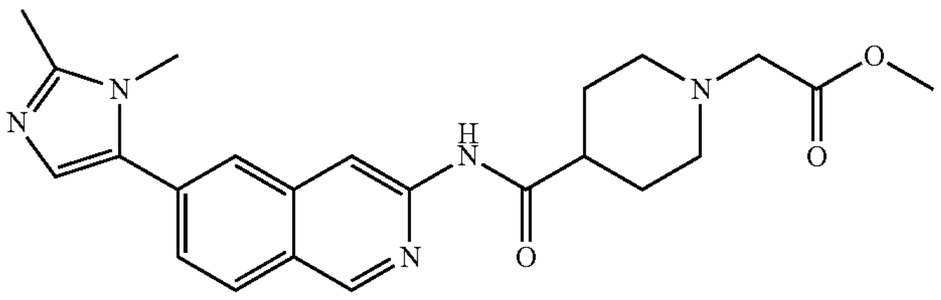

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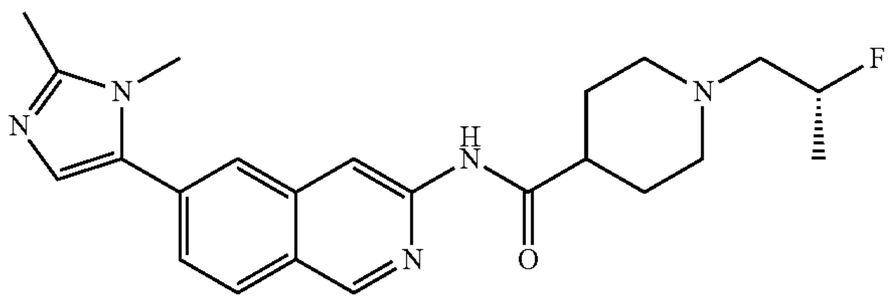

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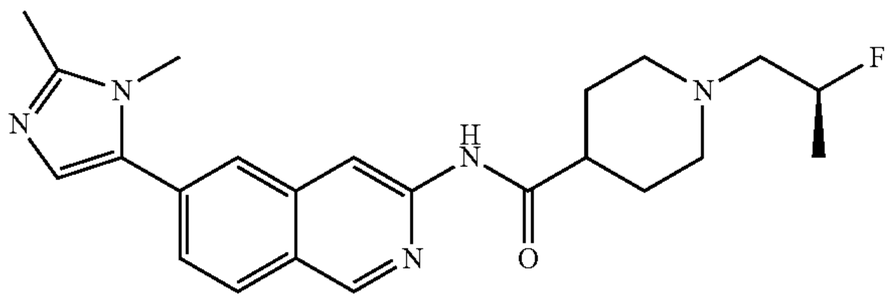

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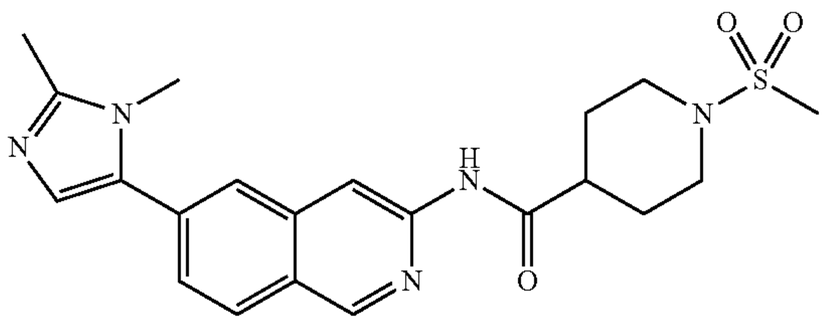

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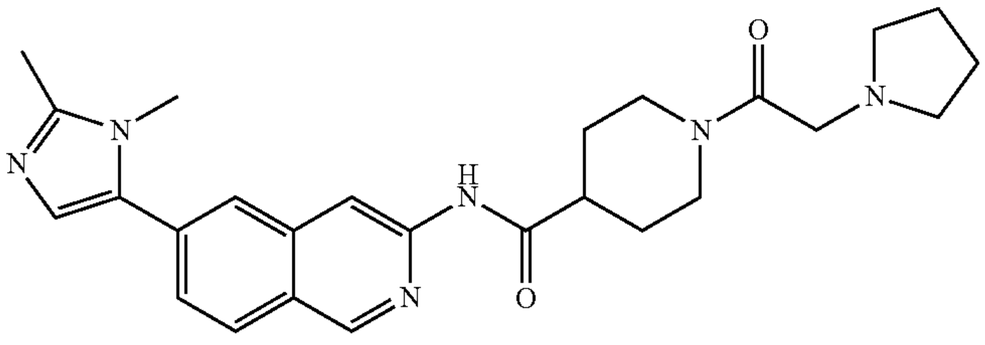

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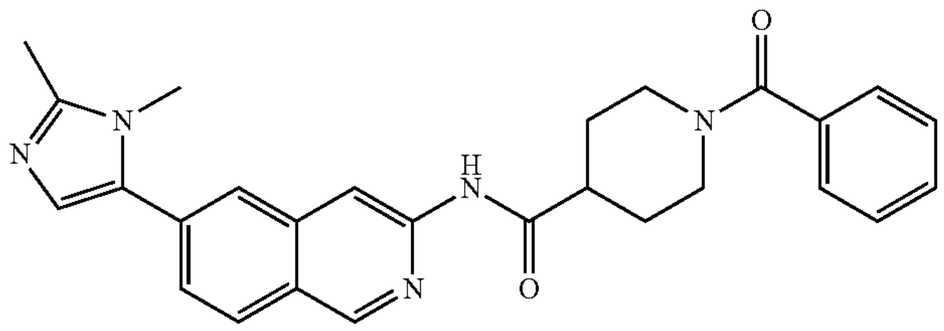
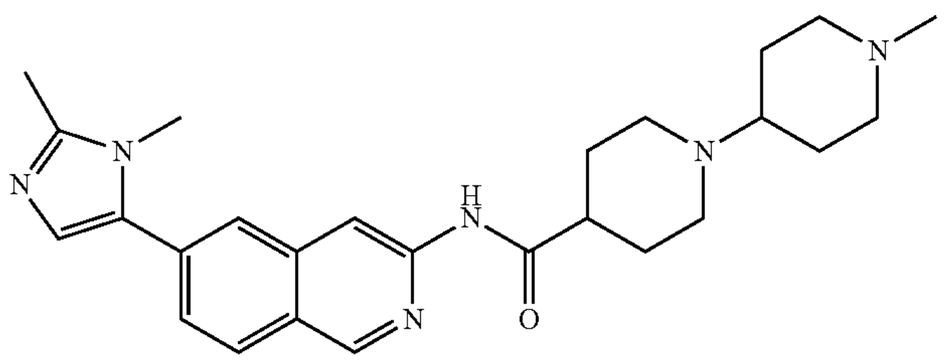
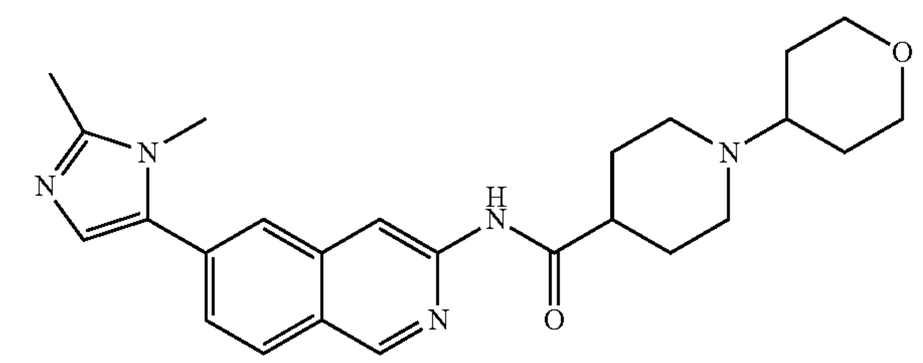
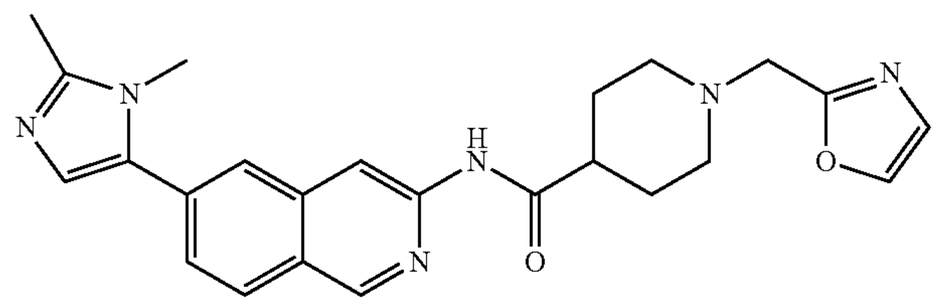
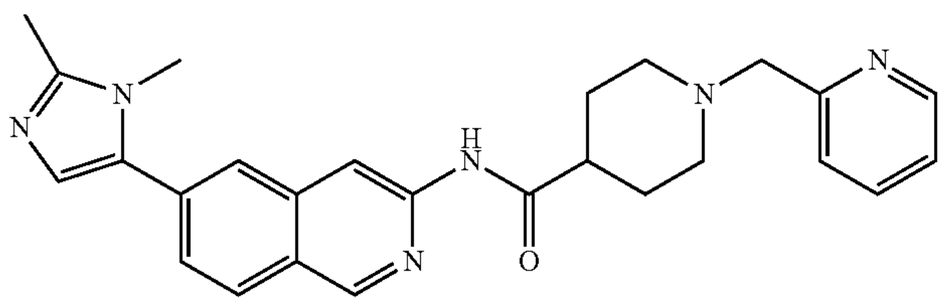
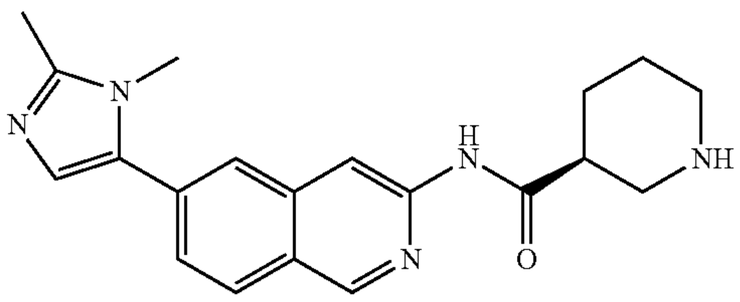
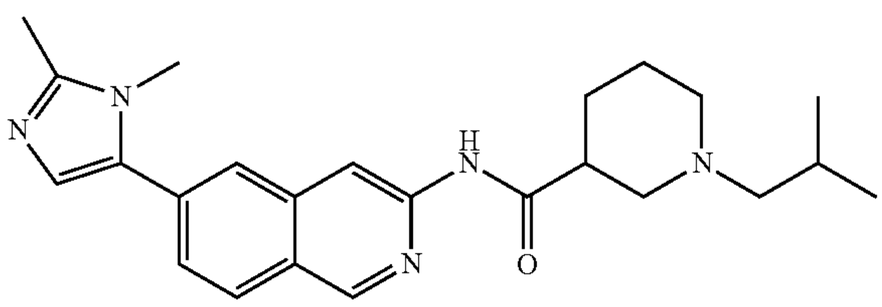
	393
	394
	395
	396
	397
	398
	399

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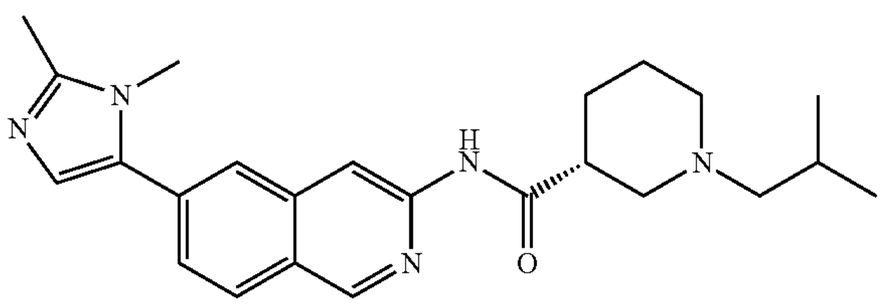

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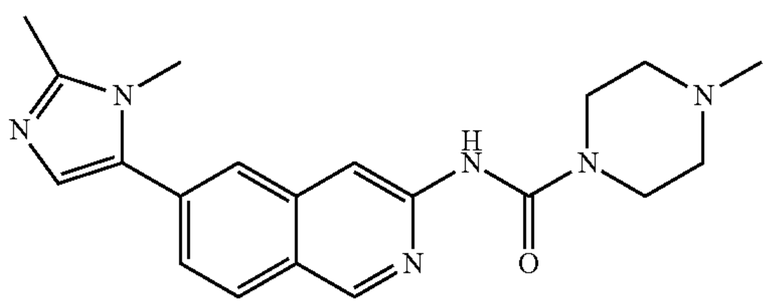

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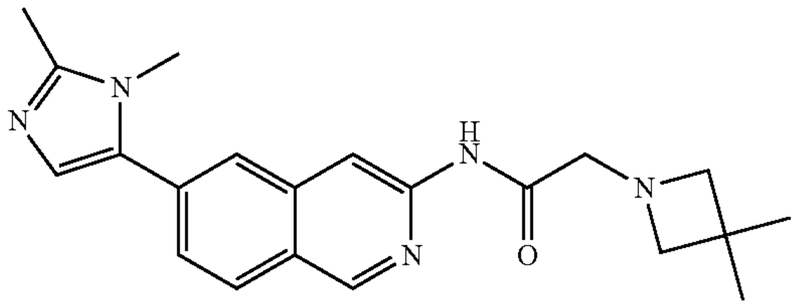

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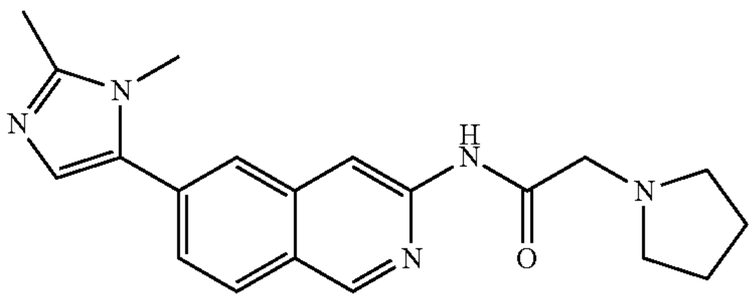

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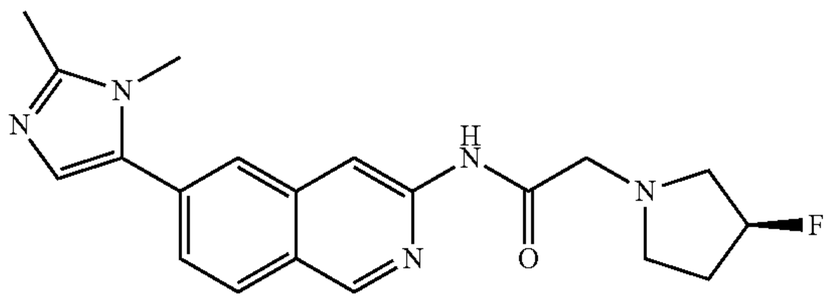

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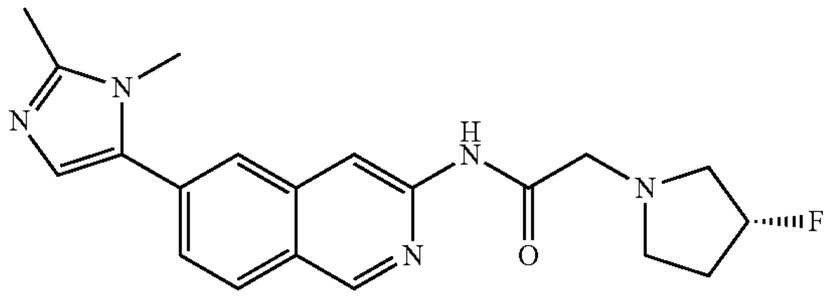

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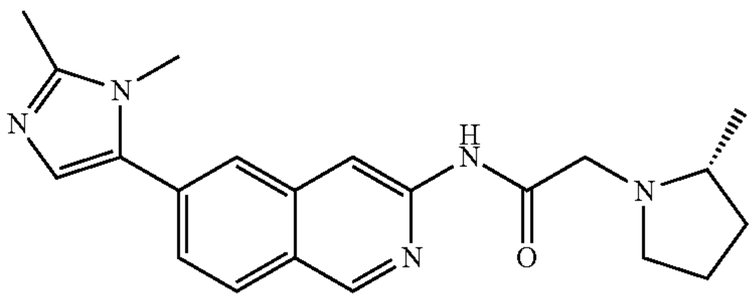

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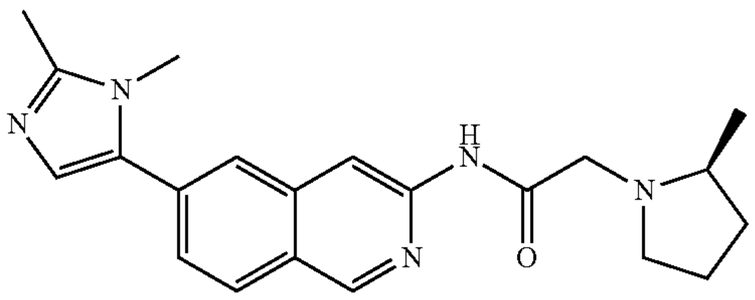

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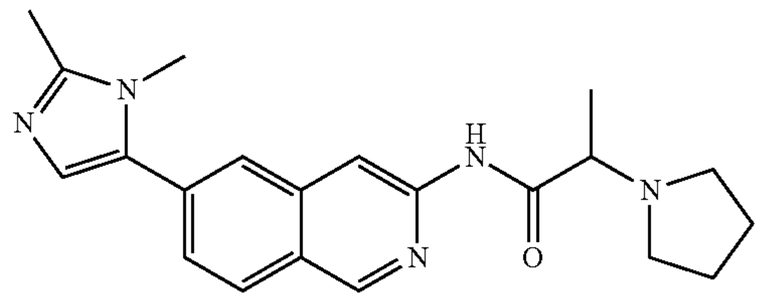
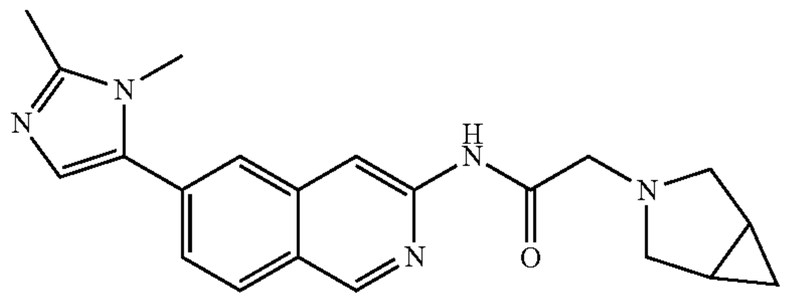
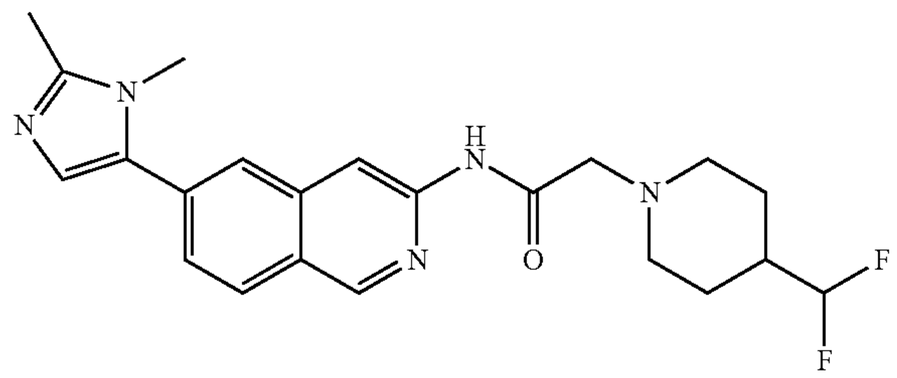
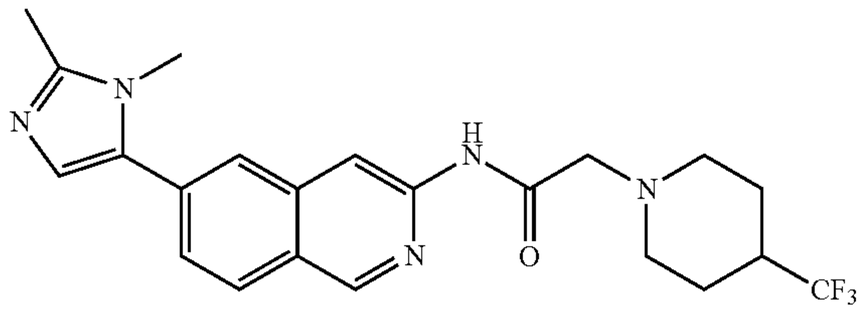
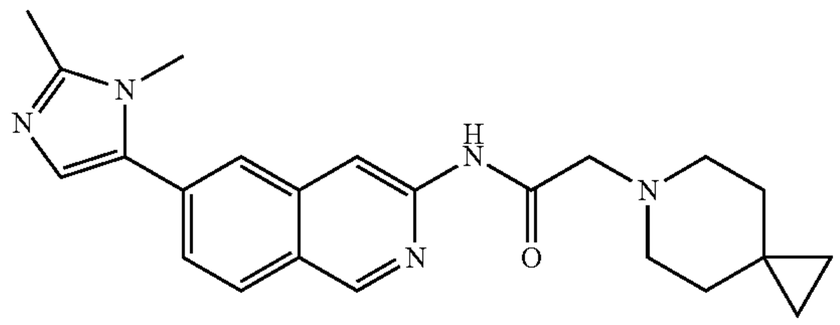
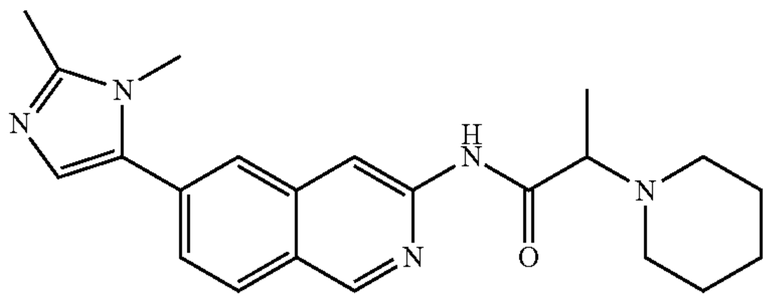
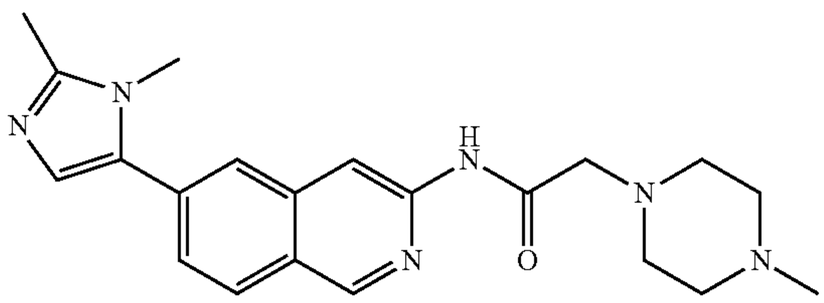
408	
409	
410	
411	
412	
413	
414	

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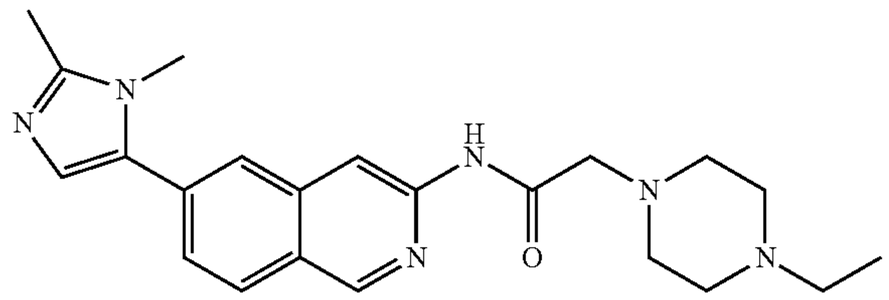
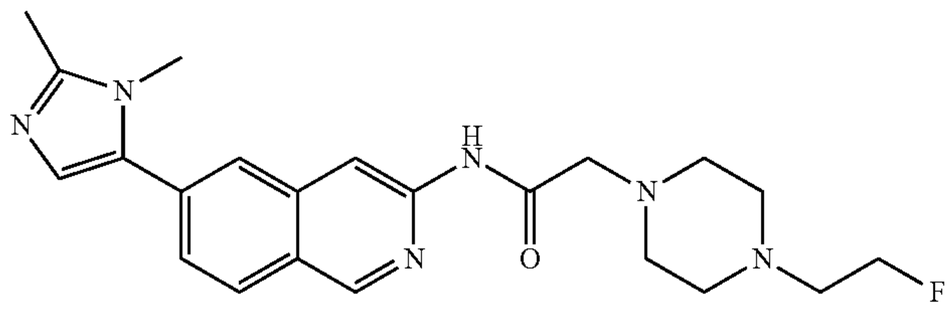
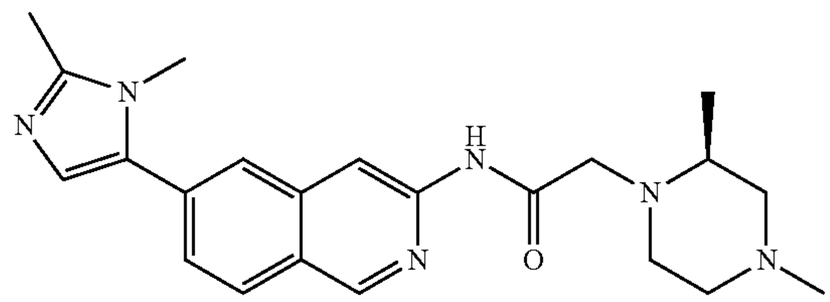
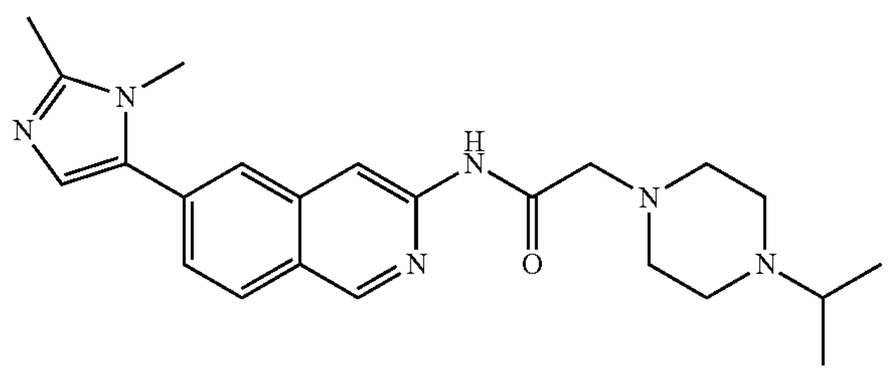
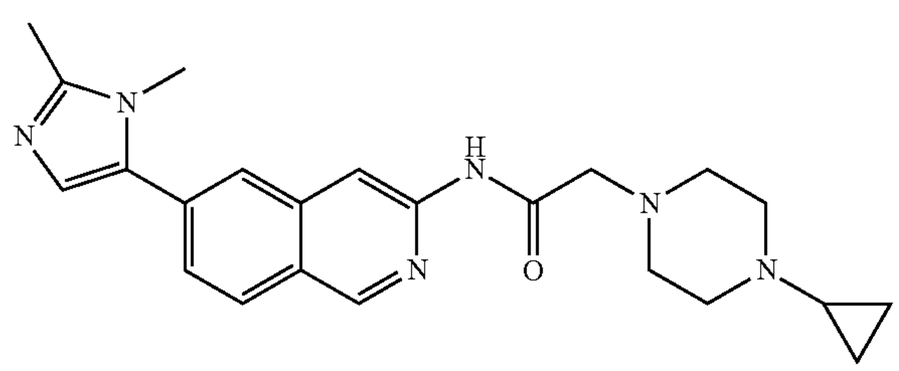
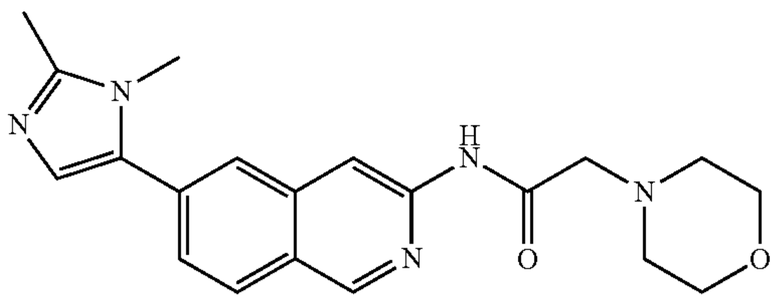
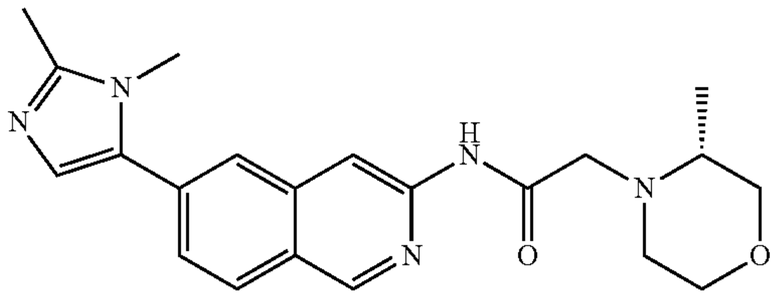
415	
416	
417	
418	
419	
420	
421	

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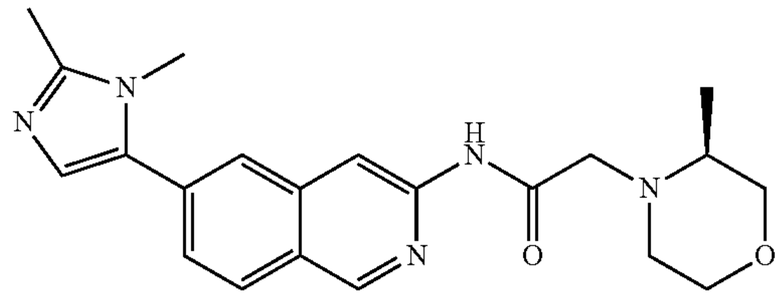
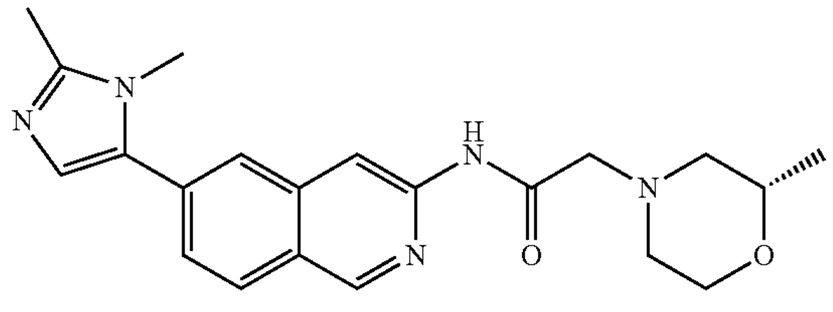
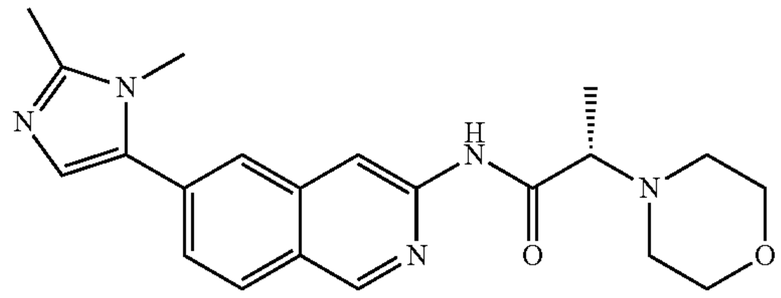
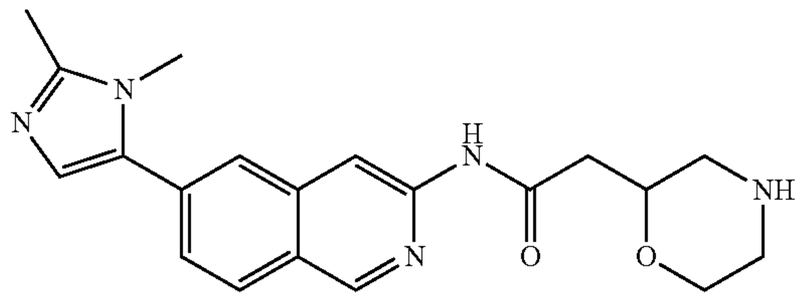
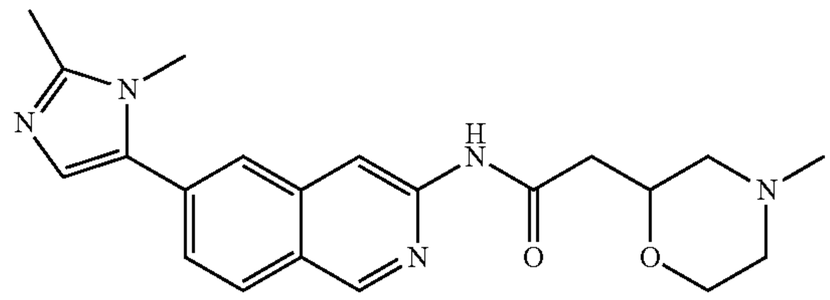
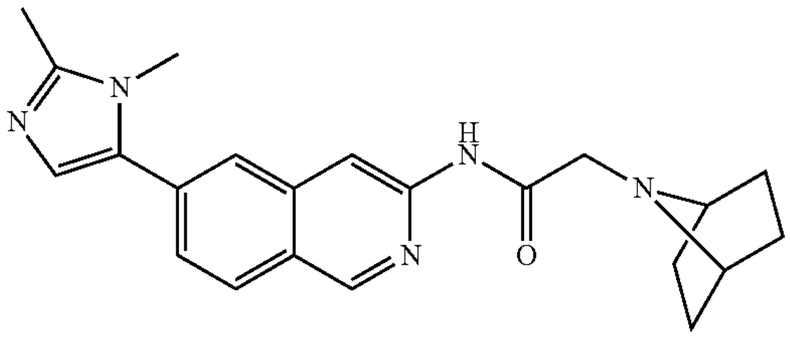
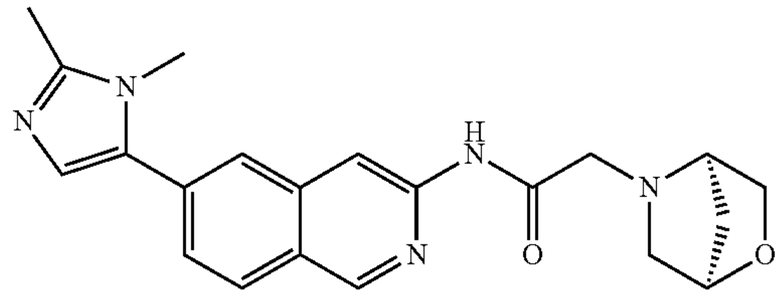
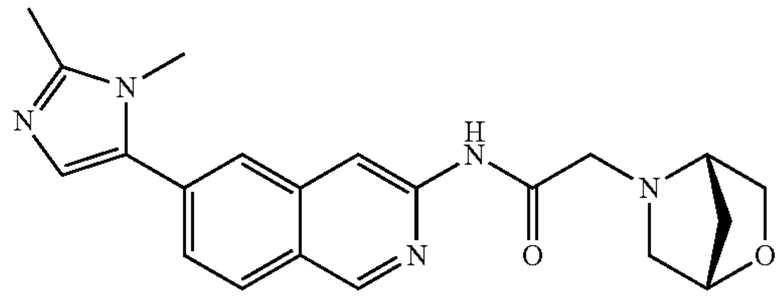
422	
423	
424	
425	
426	
427	
428	
429	

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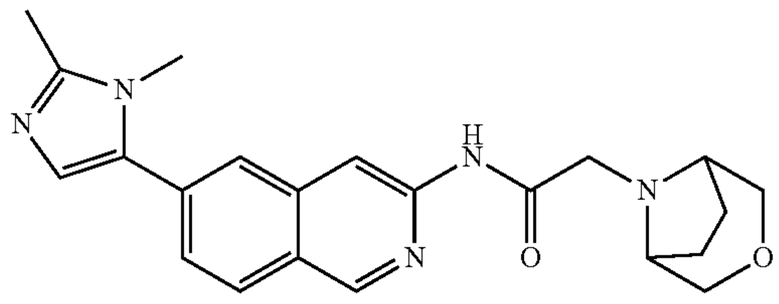
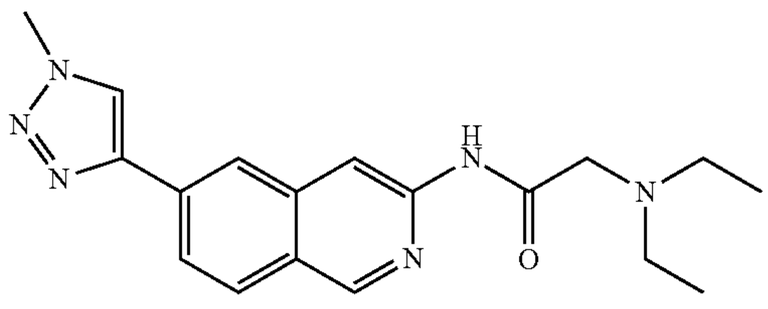
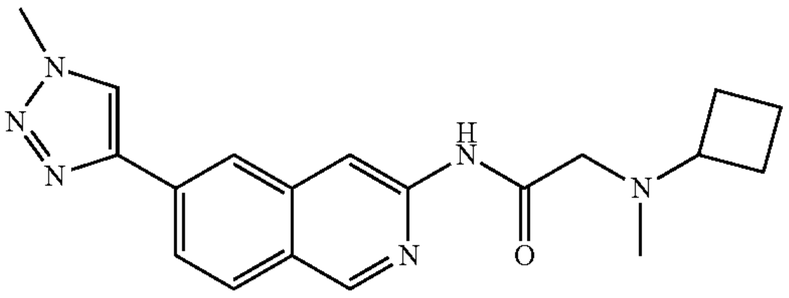
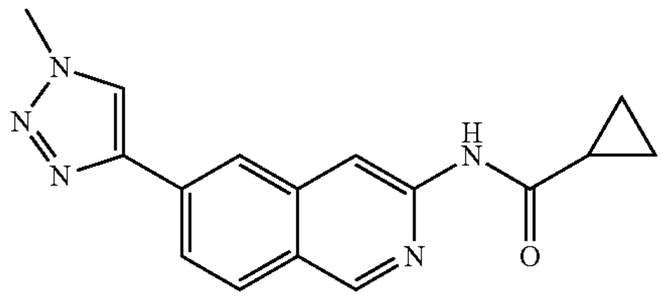
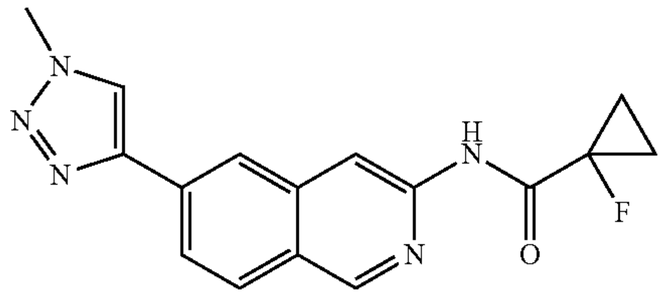
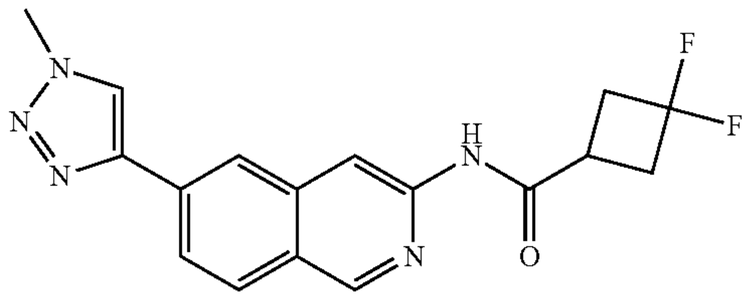
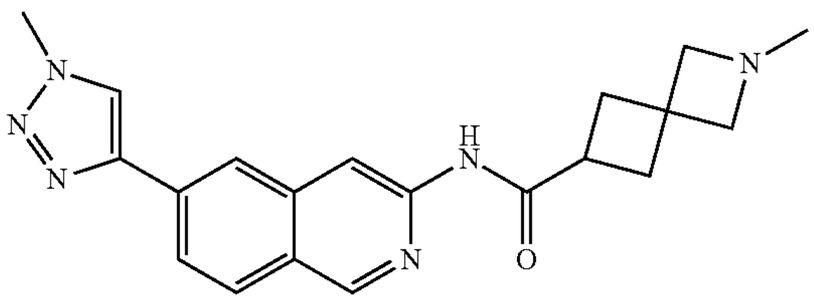
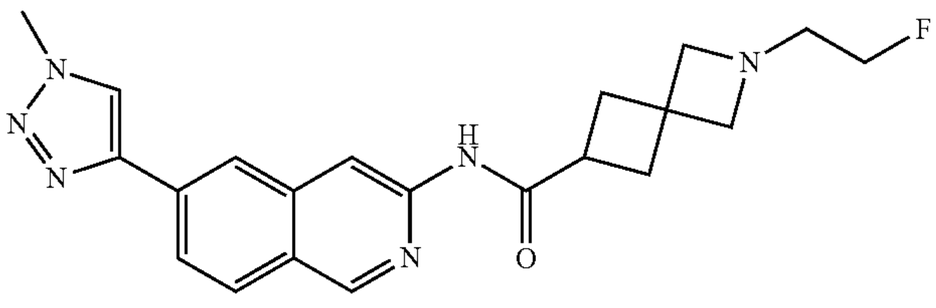
430	
431	
432	
433	
434	
435	
436	
437	

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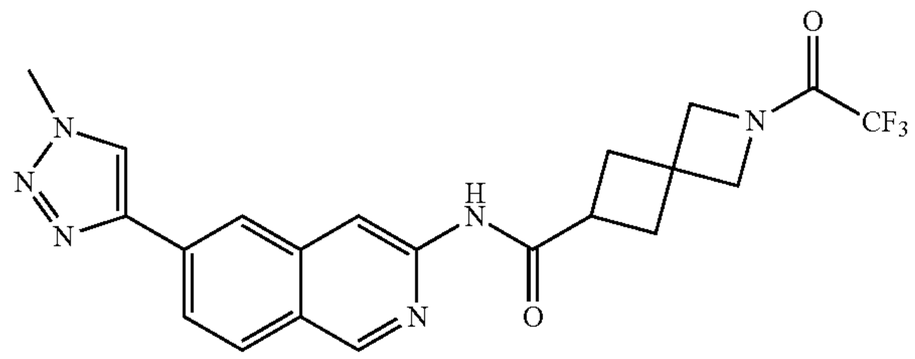
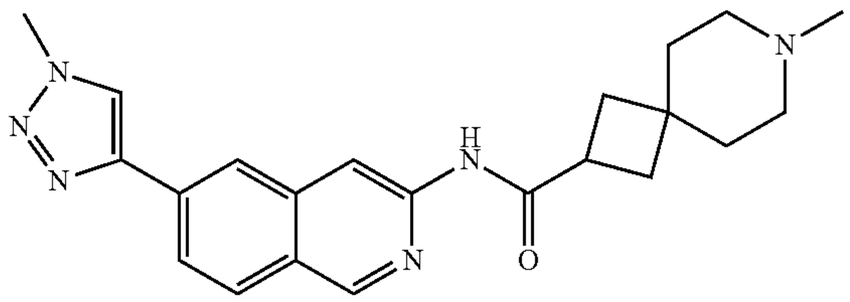
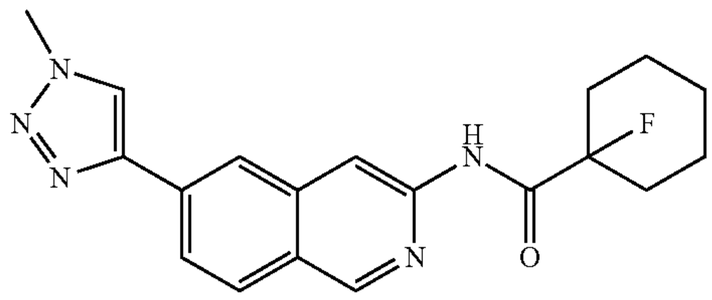
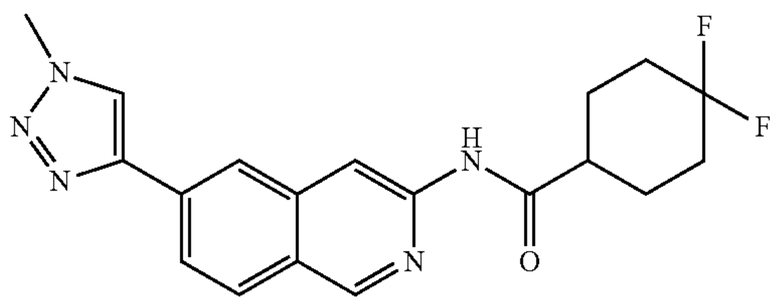
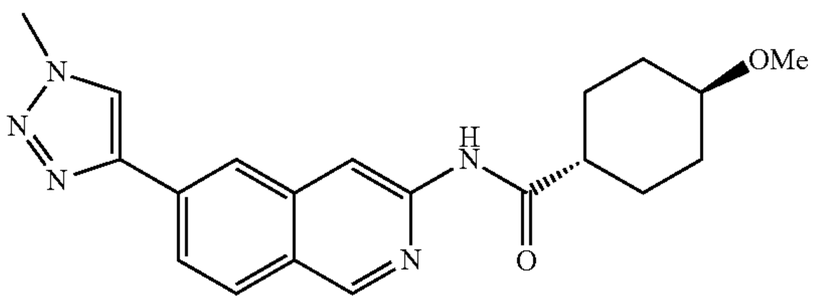
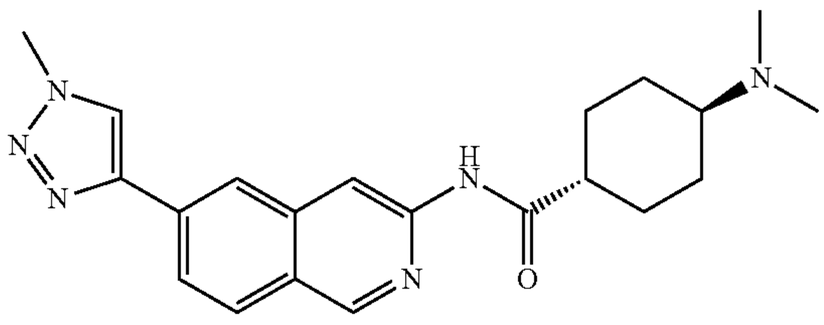
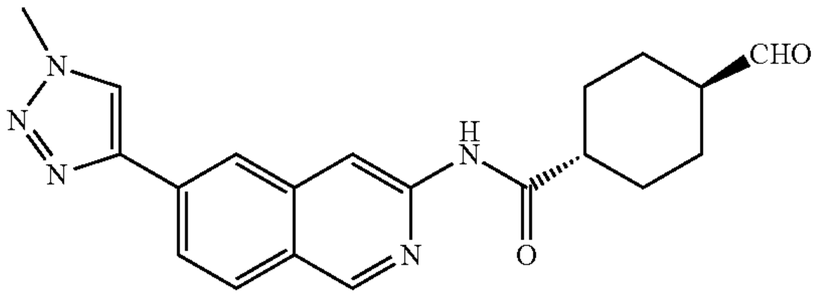
438	
439	
440	
441	
442	
443	
444	

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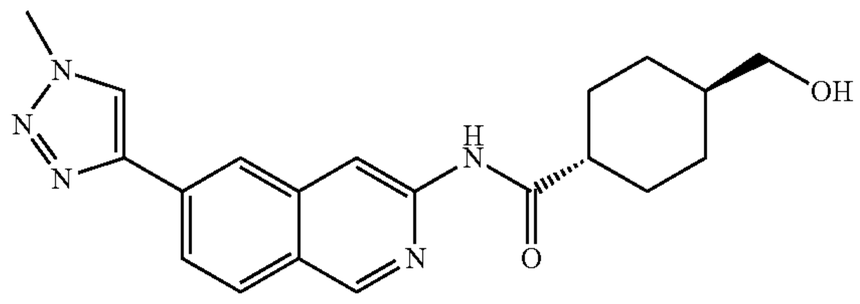
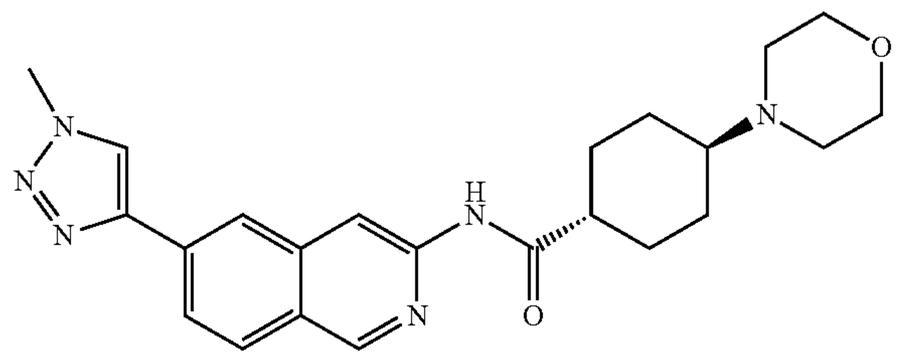
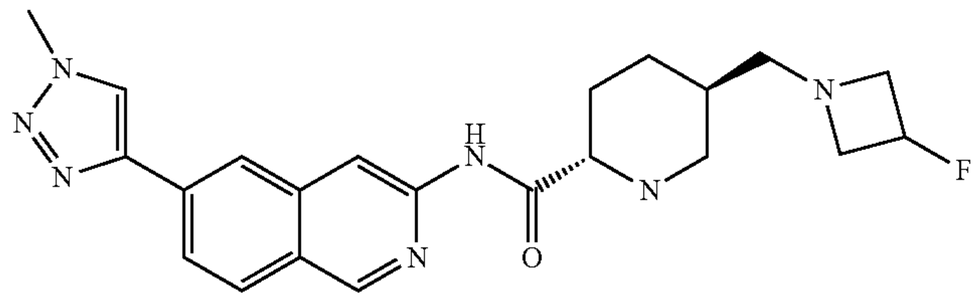
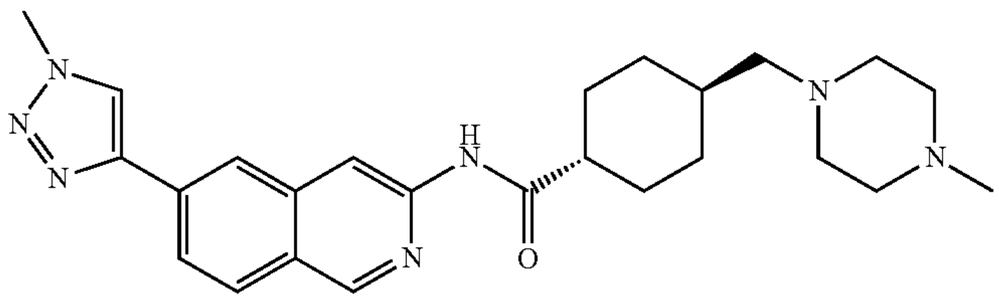
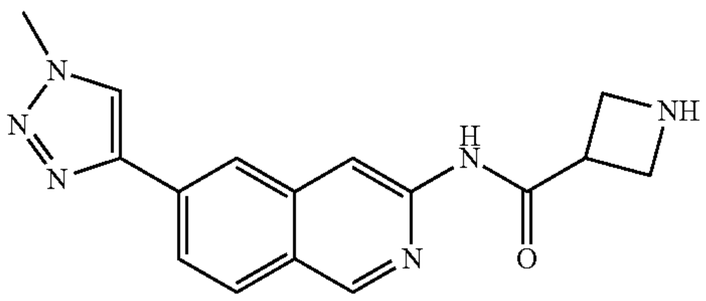
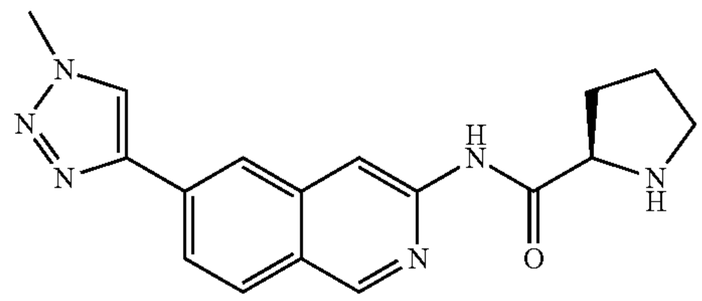
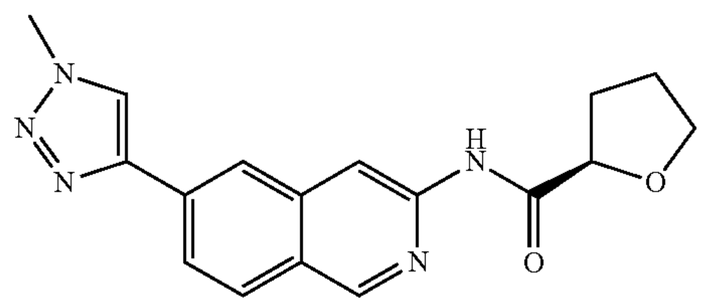
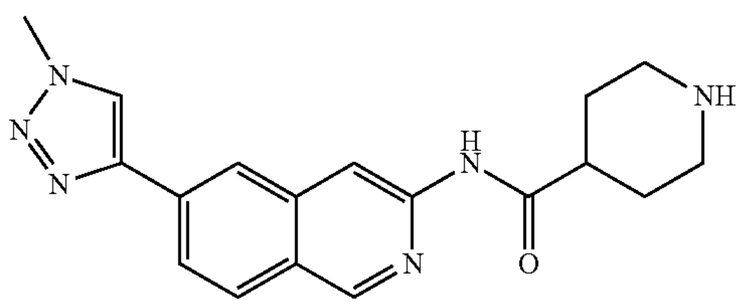
445	
446	
447	
448	
449	
450	
451	
452	

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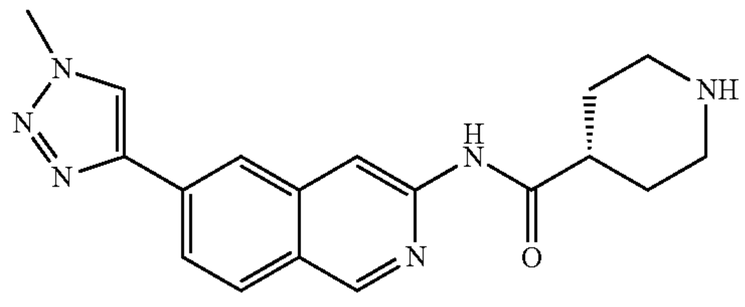
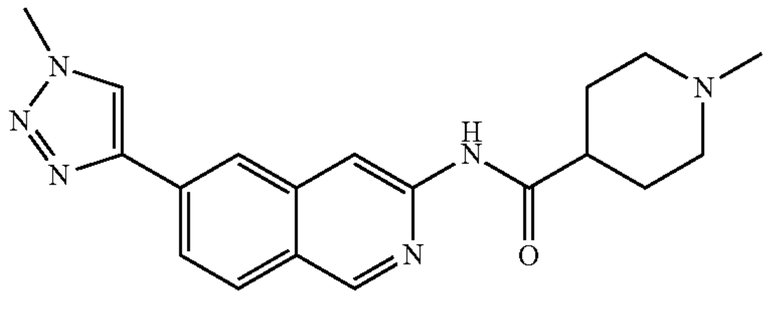
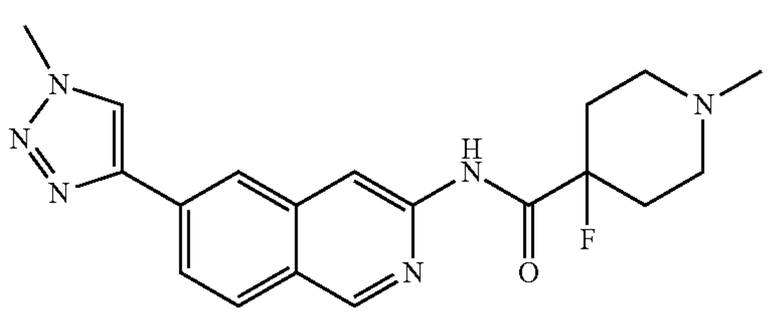
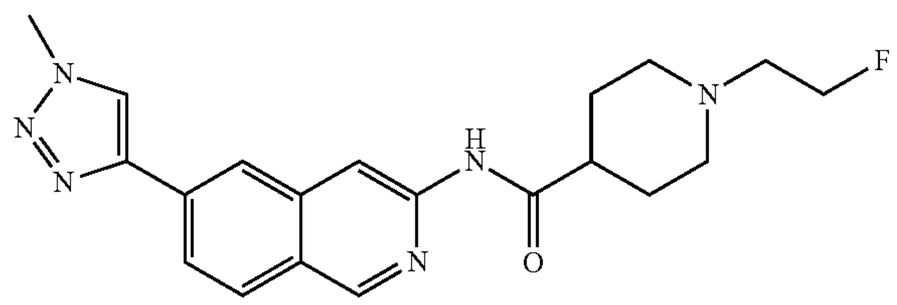
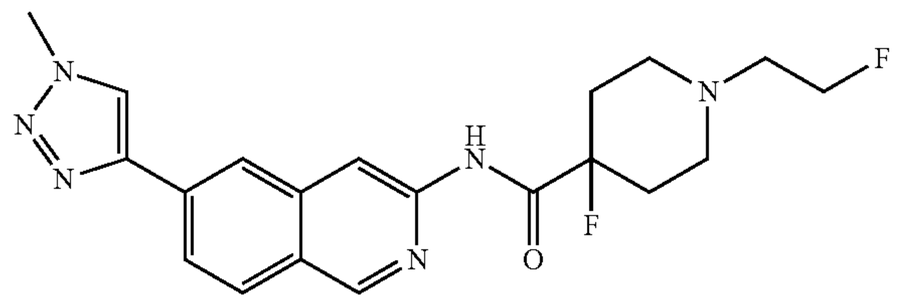
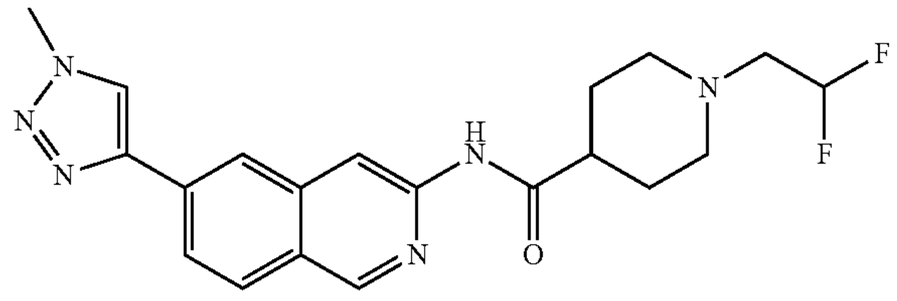
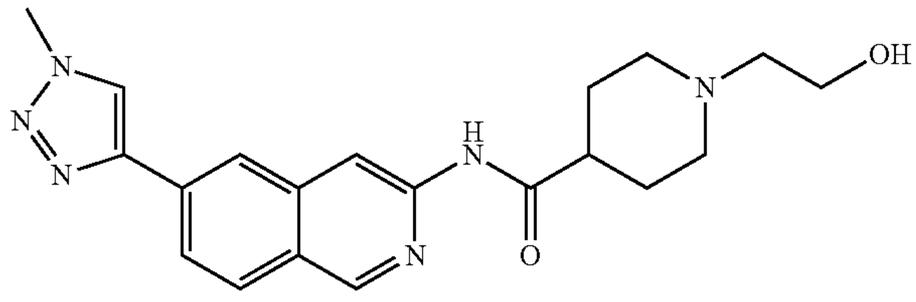
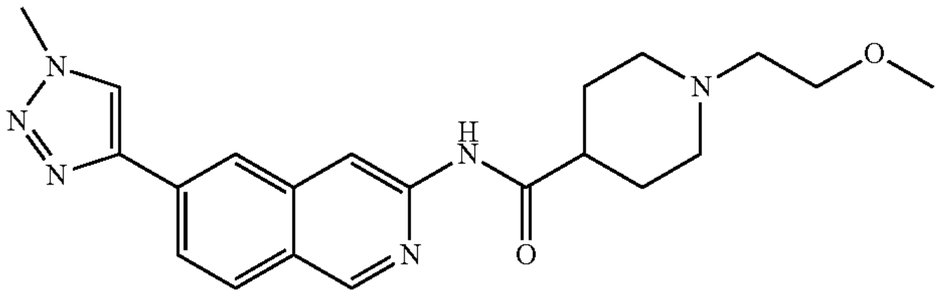
453	
454	
455	
456	
457	
458	
459	
460	

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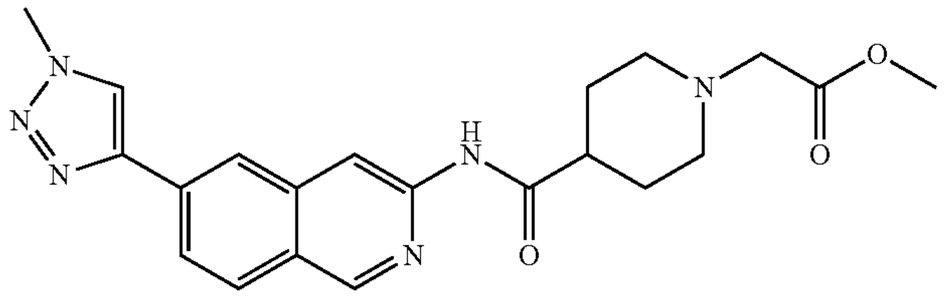
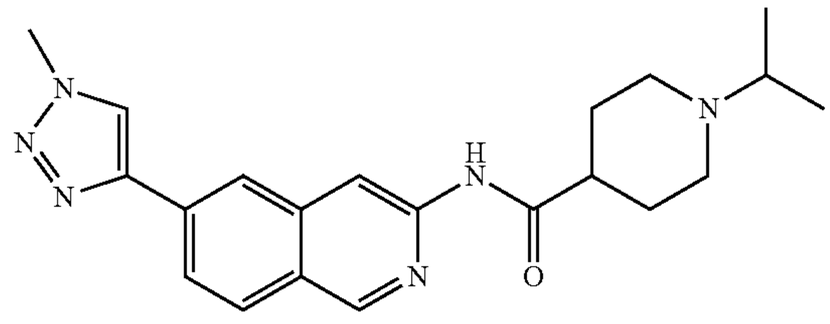
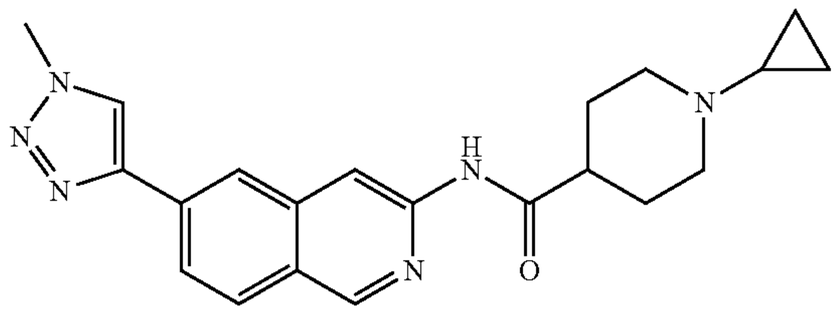
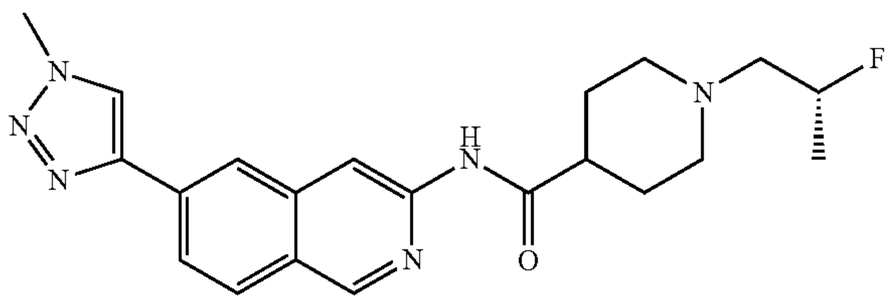
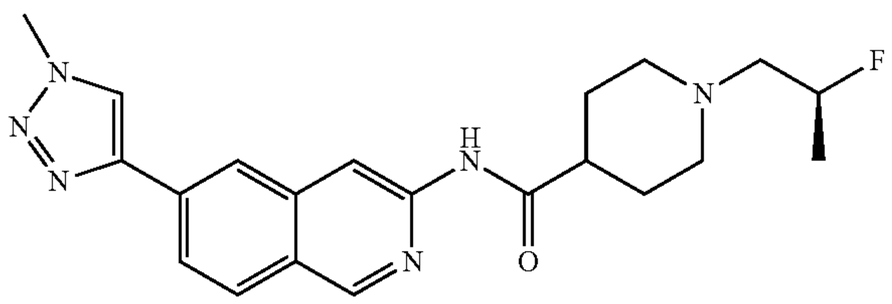
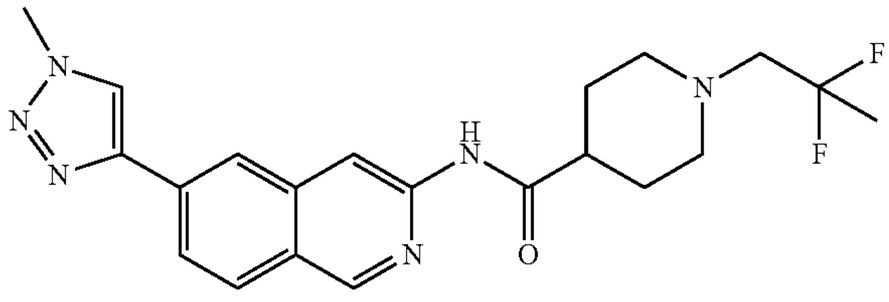
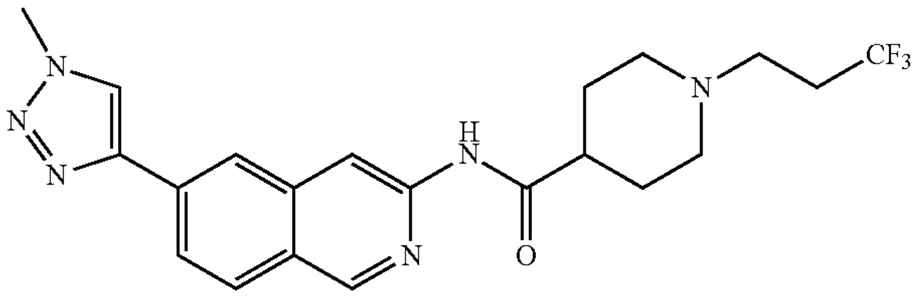
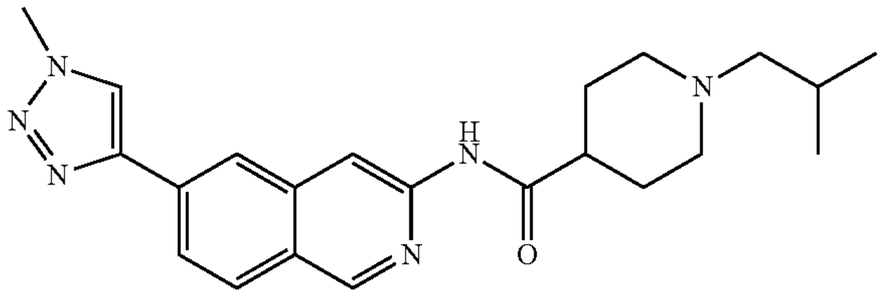
461	
462	
463	
464	
465	
466	
467	
468	

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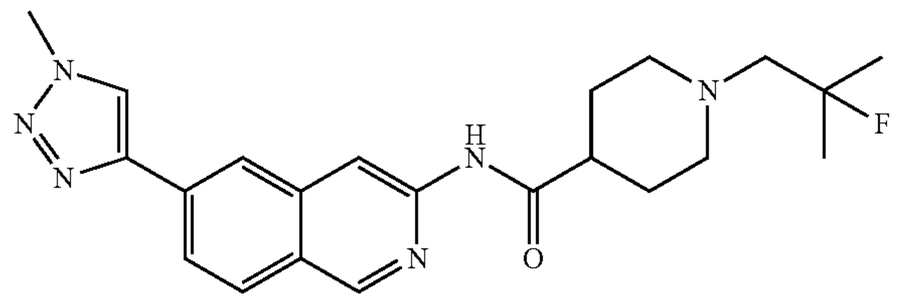
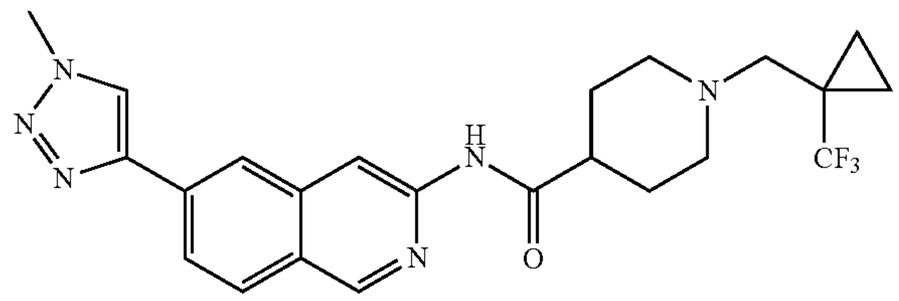
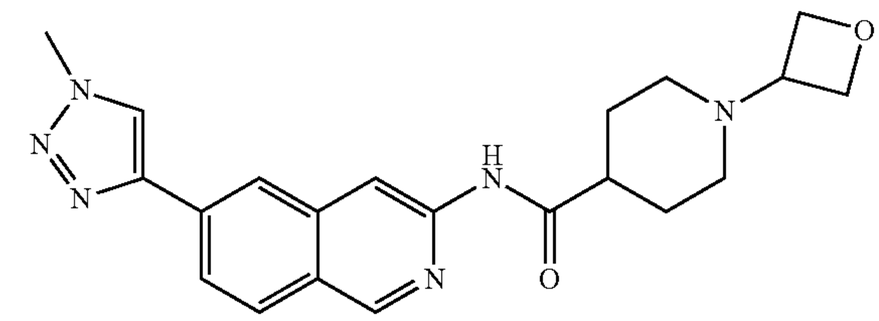
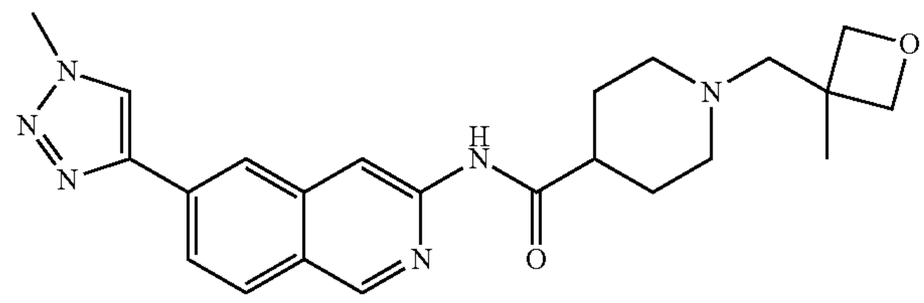
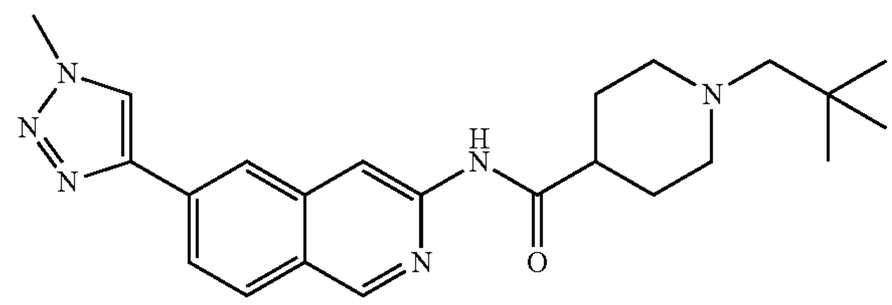
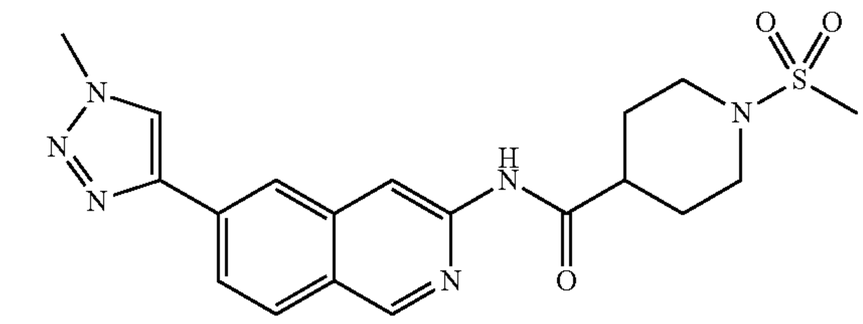
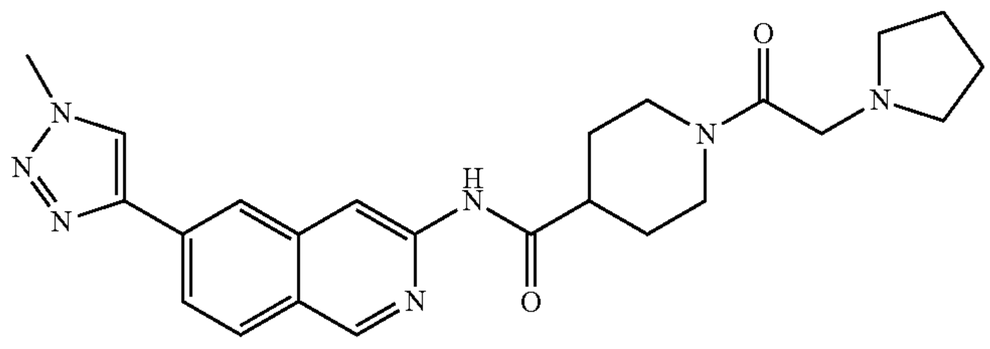
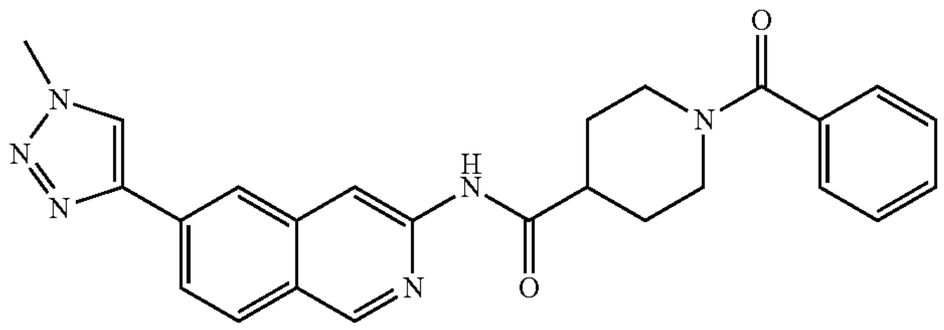
469	
470	
471	
472	
473	
474	
475	

TABLE 1-continued

476



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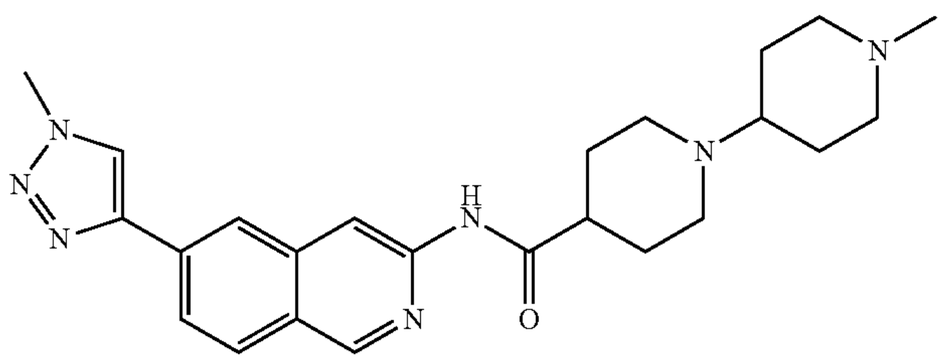

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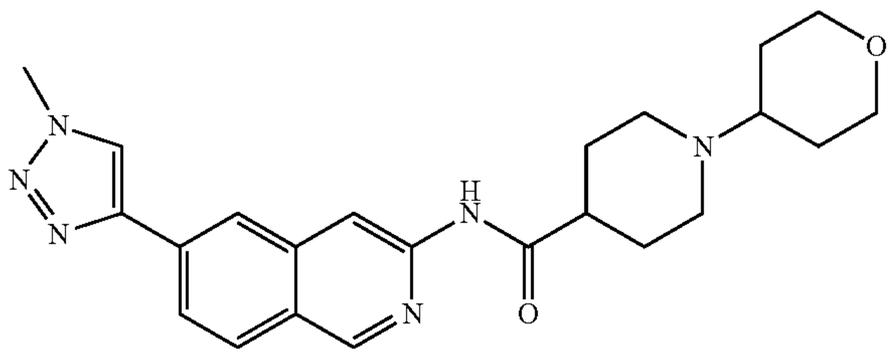

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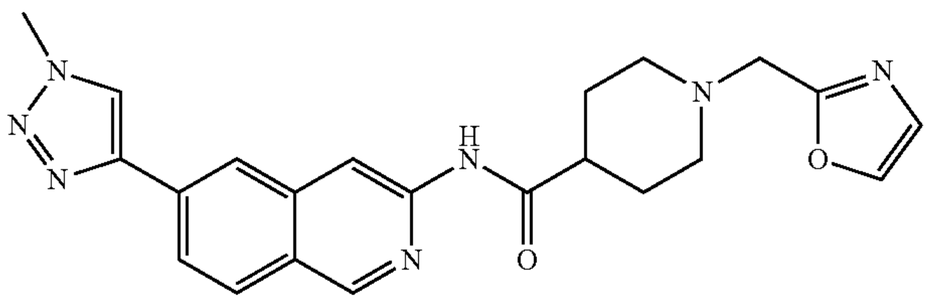

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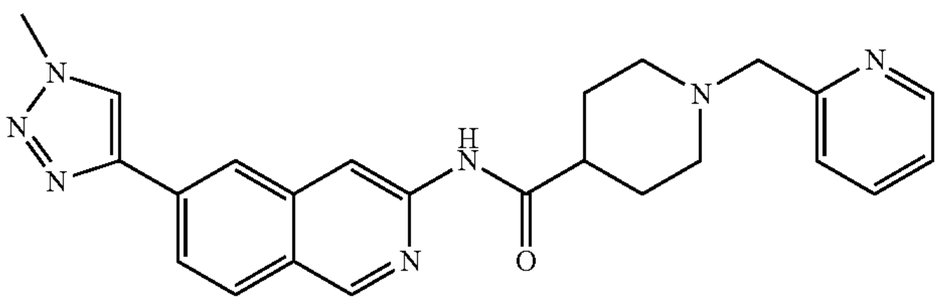

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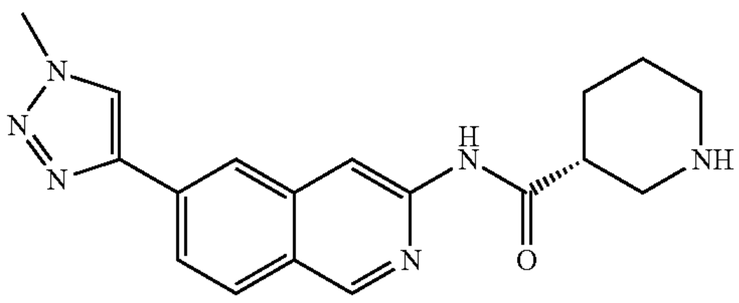

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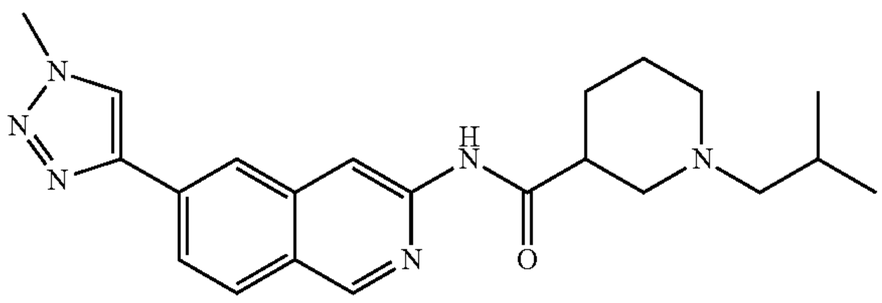
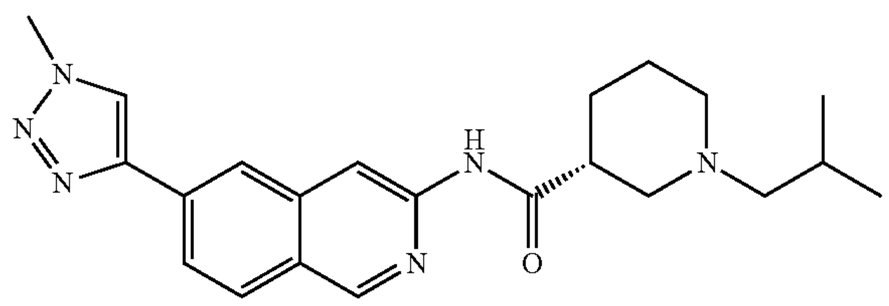


TABLE 1-continued

	483
	
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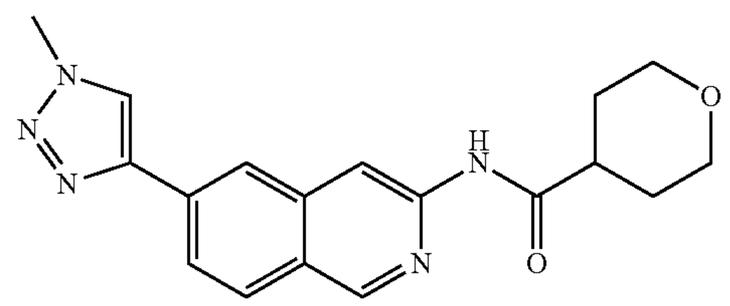	
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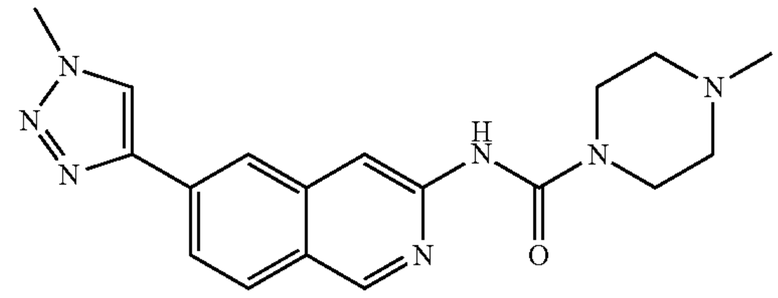	
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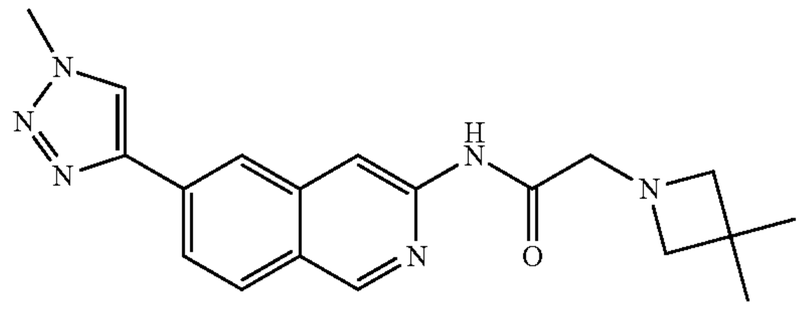	
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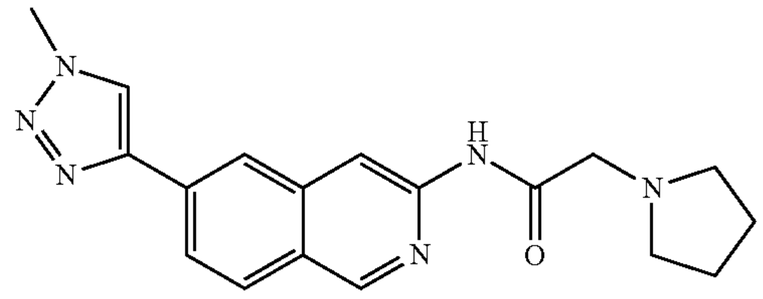	
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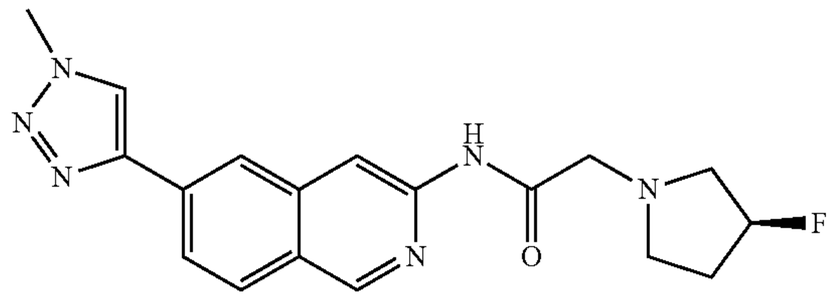	
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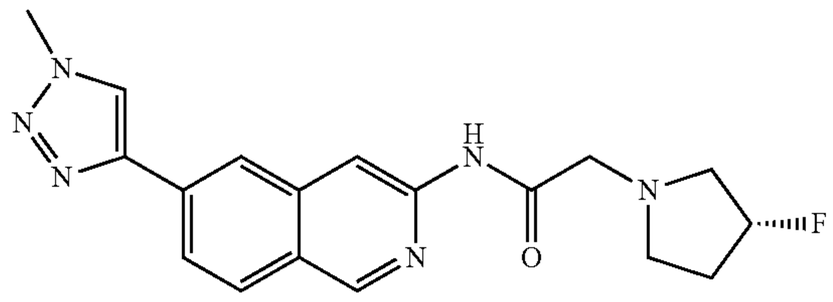	
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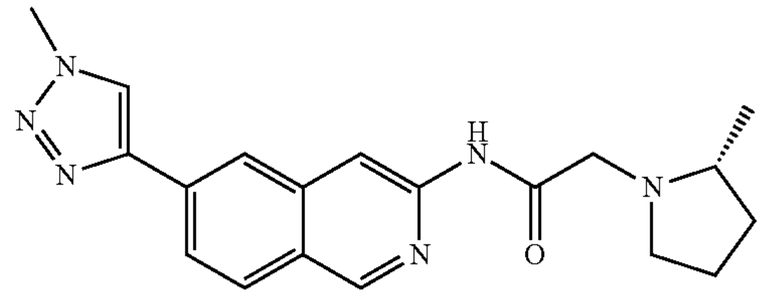	

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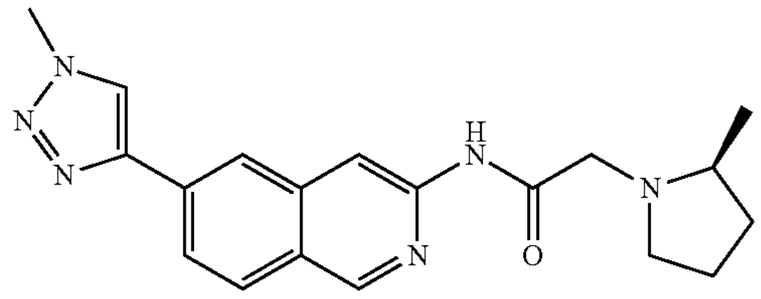
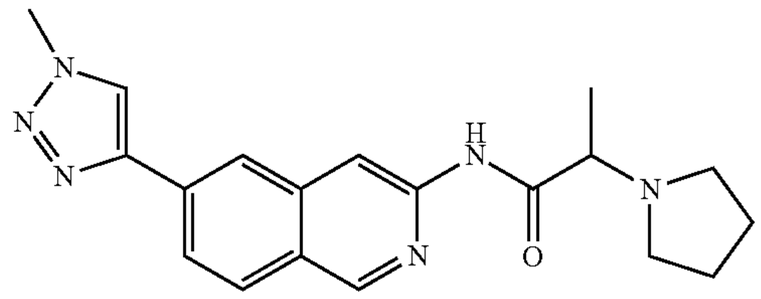
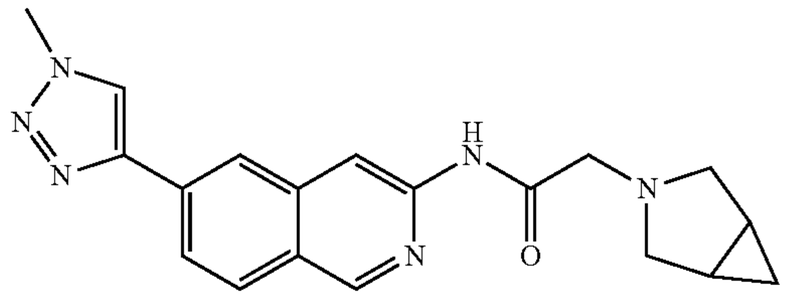
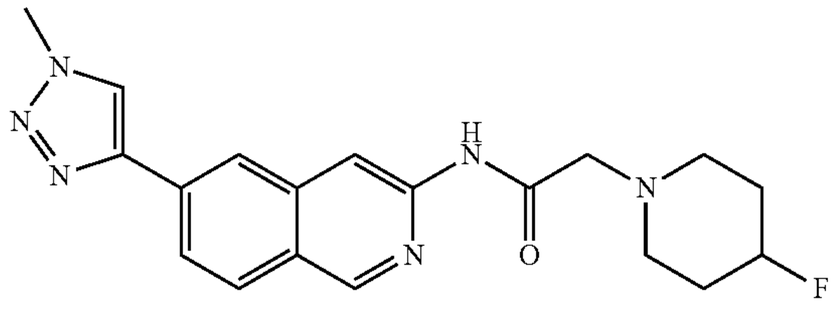
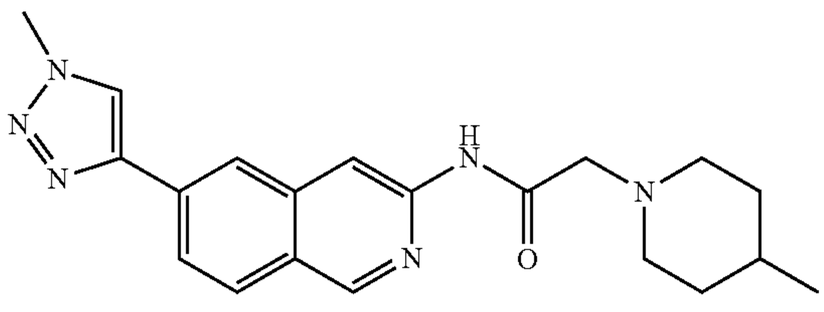
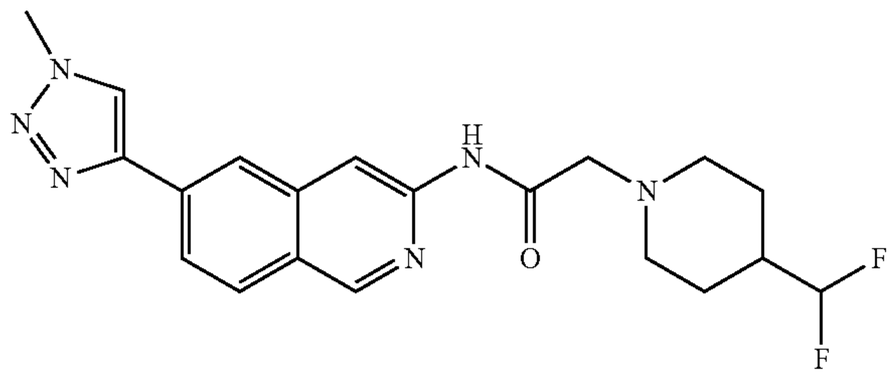
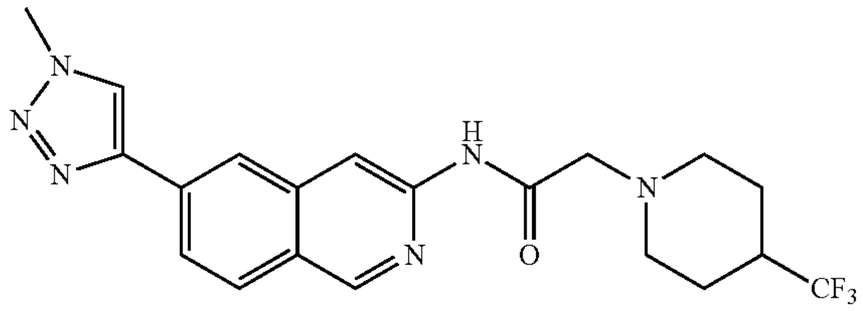
491	
492	
493	
494	
495	
496	
497	

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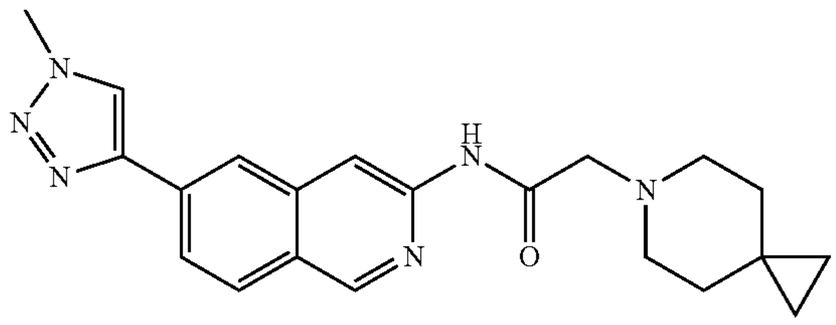
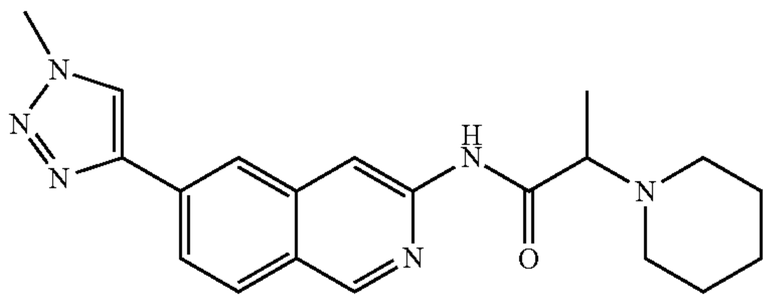
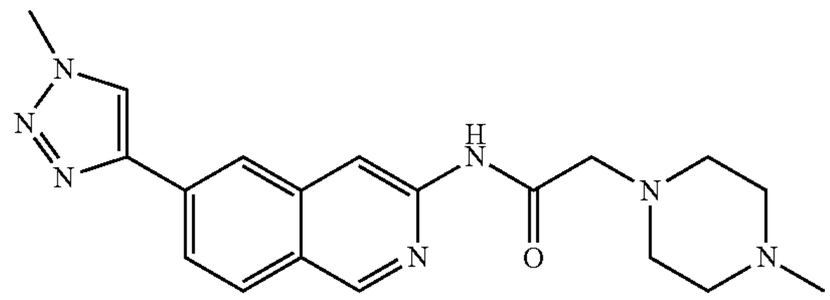
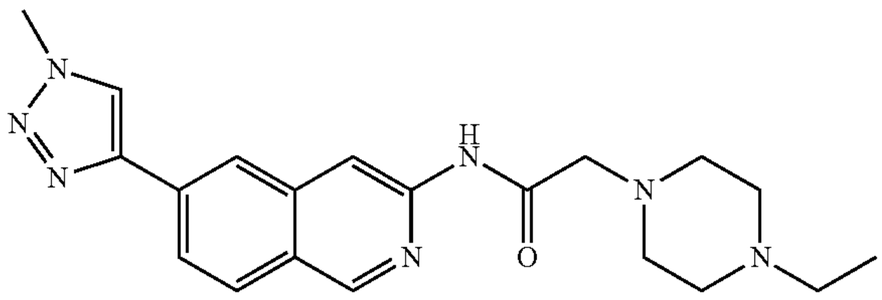
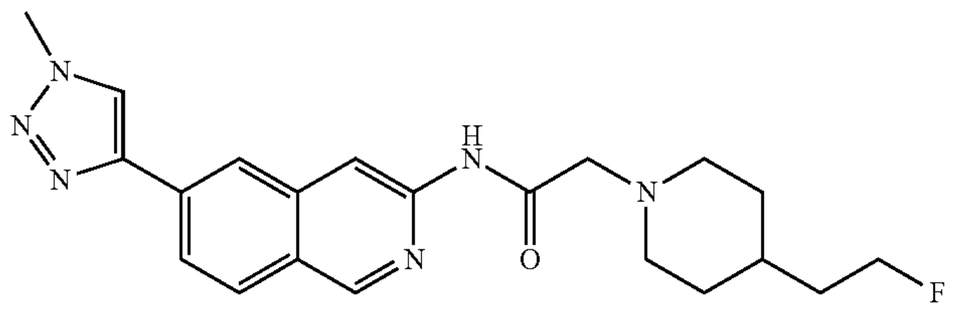
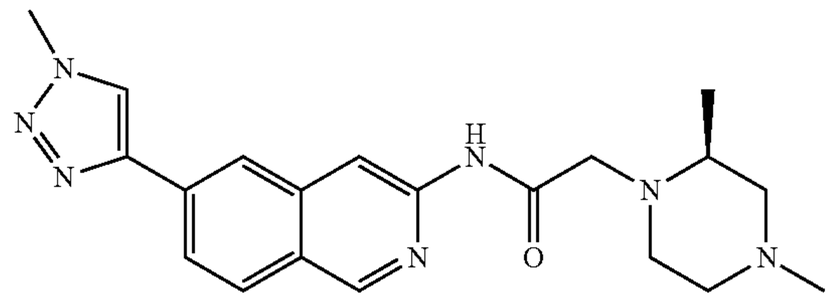
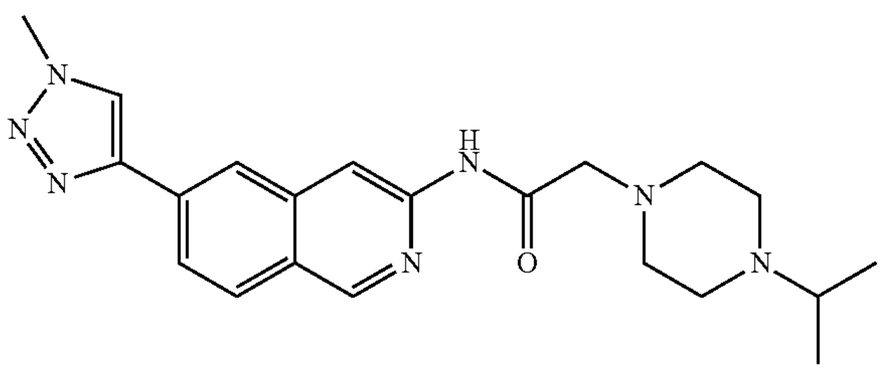
498	
499	
500	
501	
502	
503	
504	

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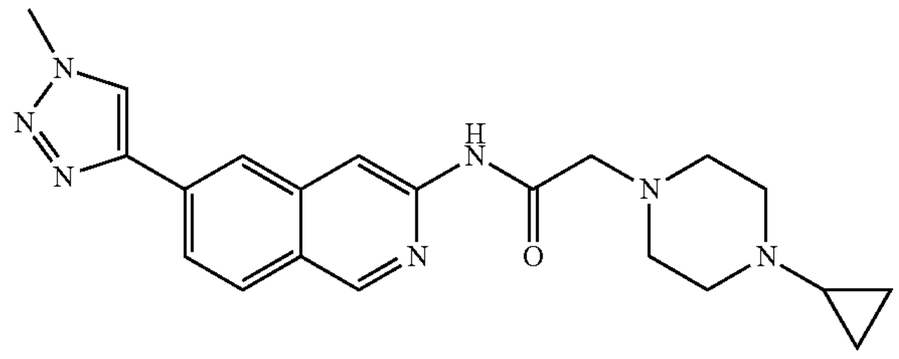
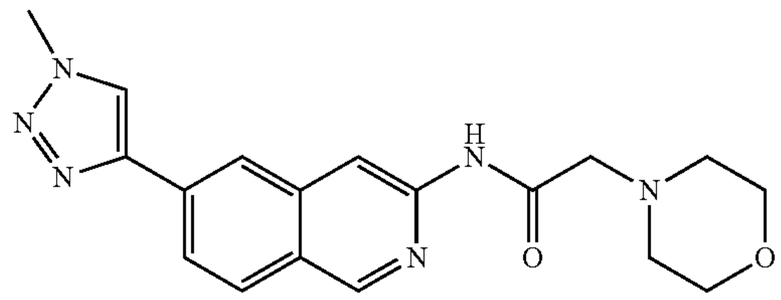
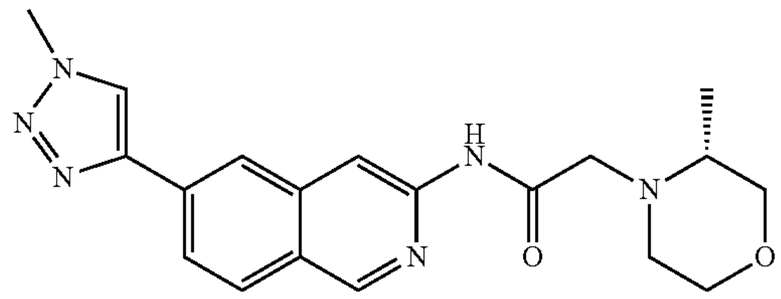
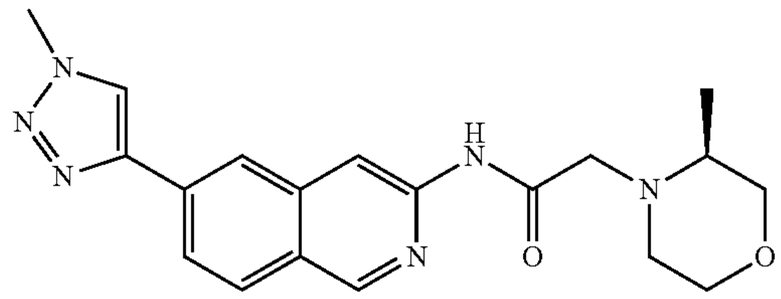
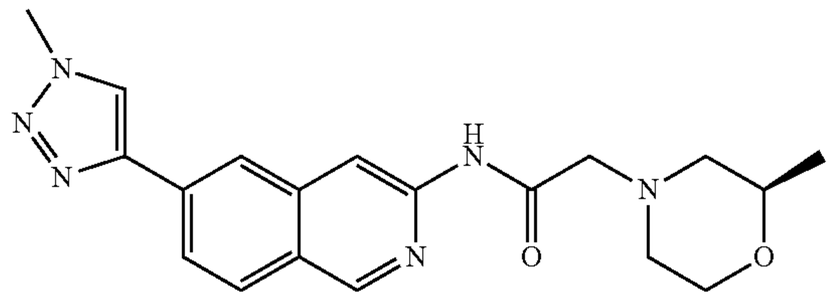
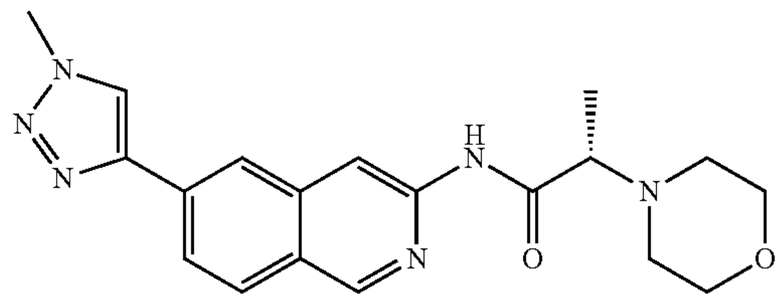
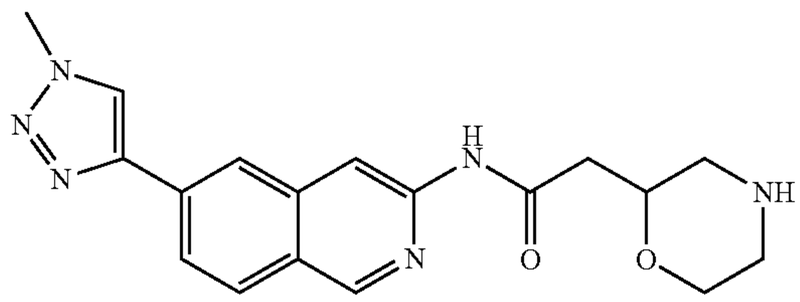
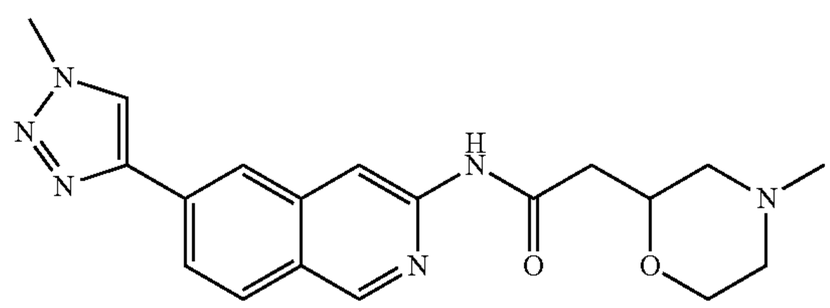
505	
506	
507	
508	
509	
510	
511	
512	

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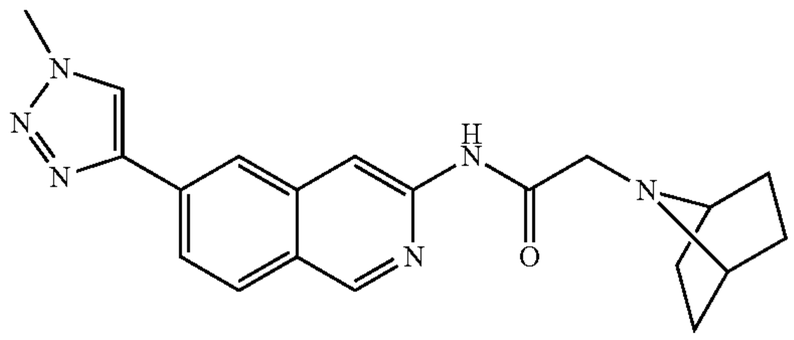
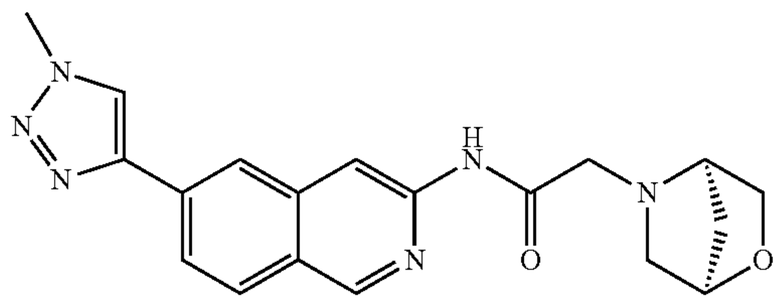
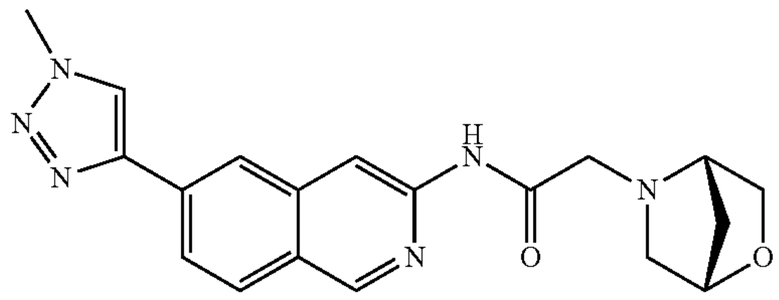
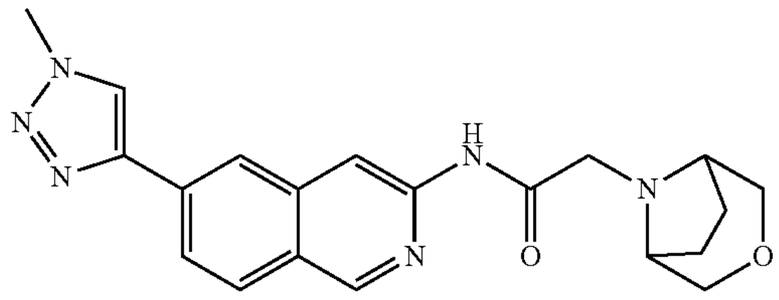
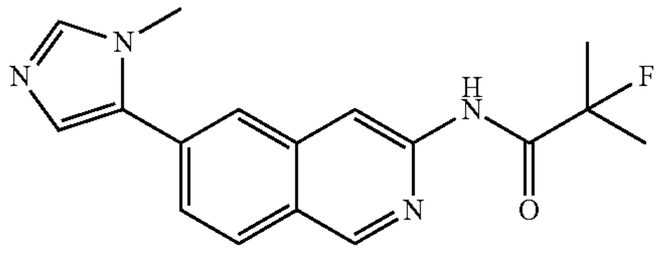
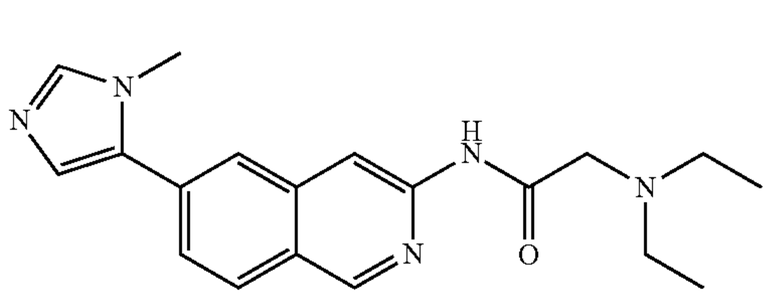
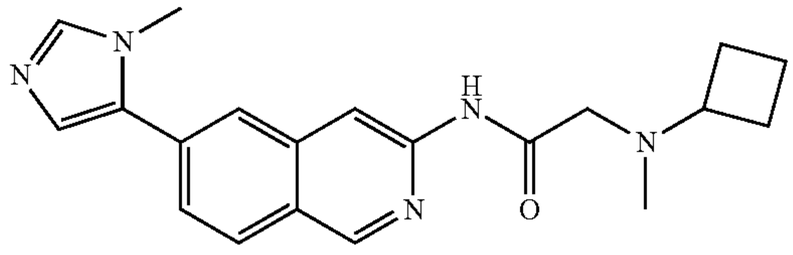
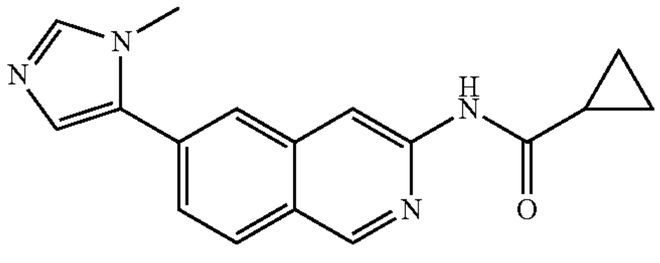
513	
514	
515	
516	
517	
518	
519	
520	

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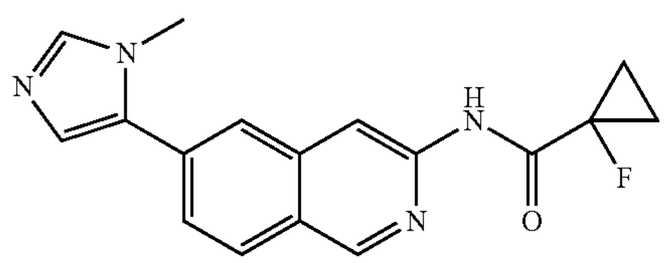
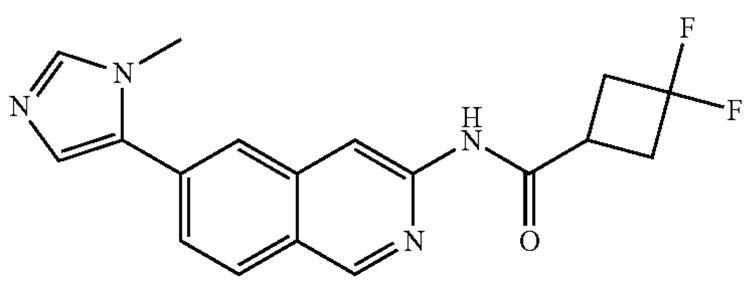
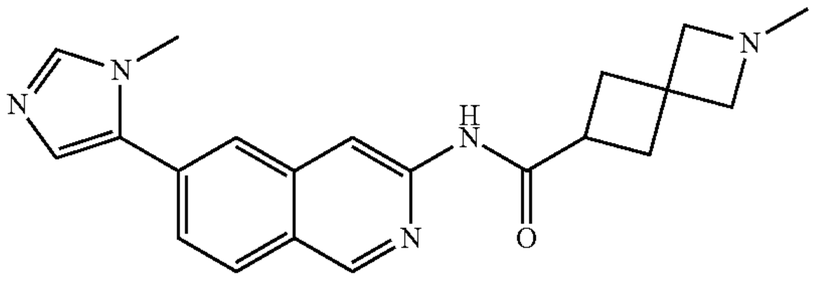
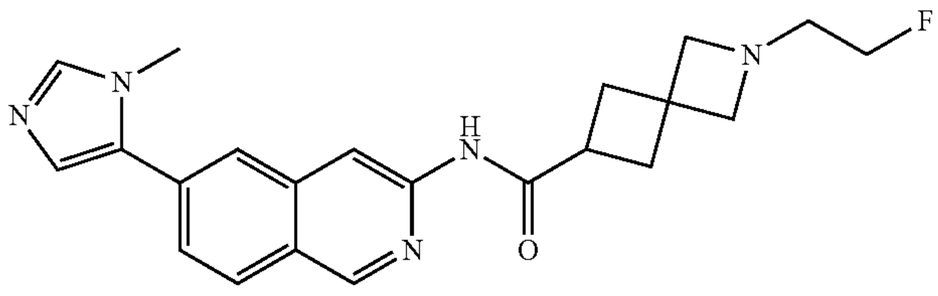
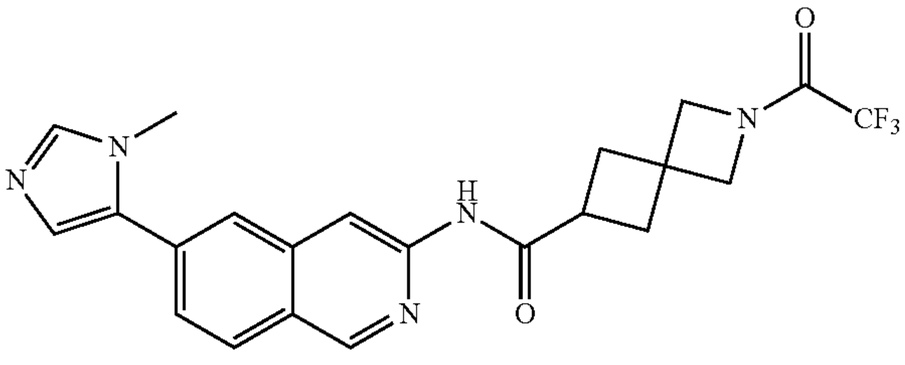
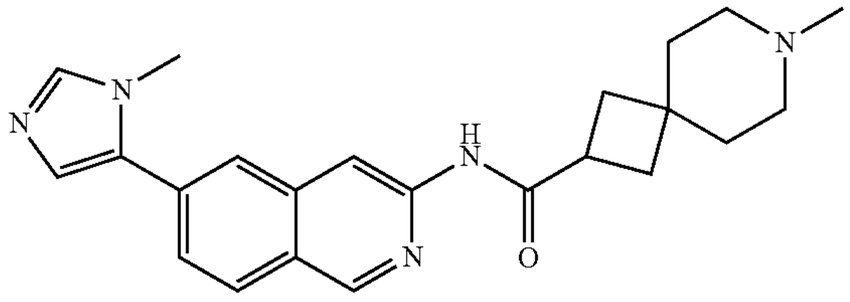
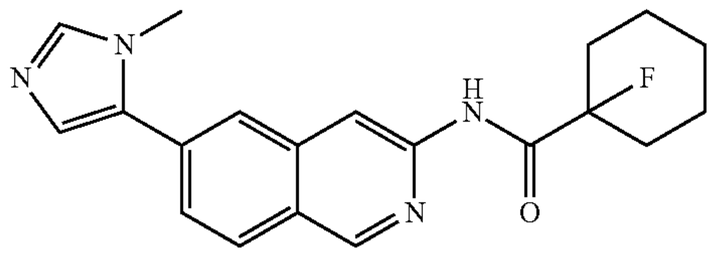
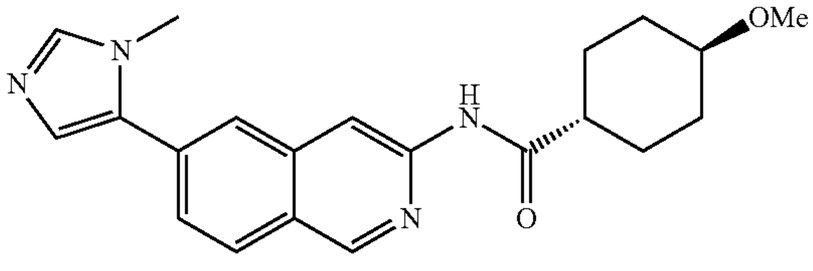
	521
	522
	523
	524
	525
	526
	527
	528

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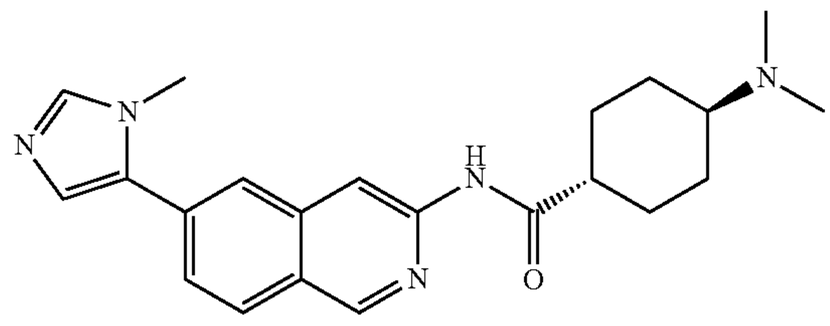

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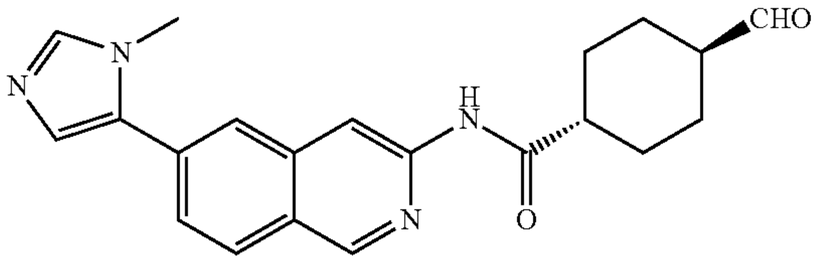

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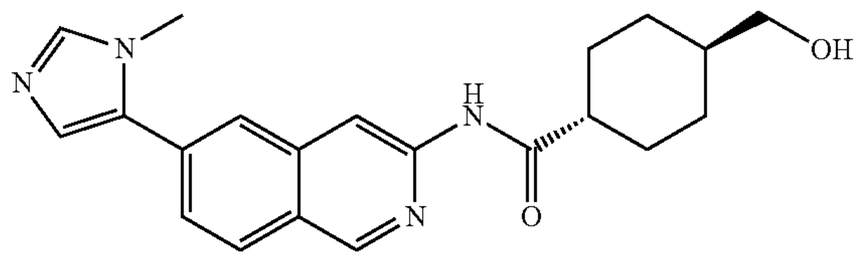

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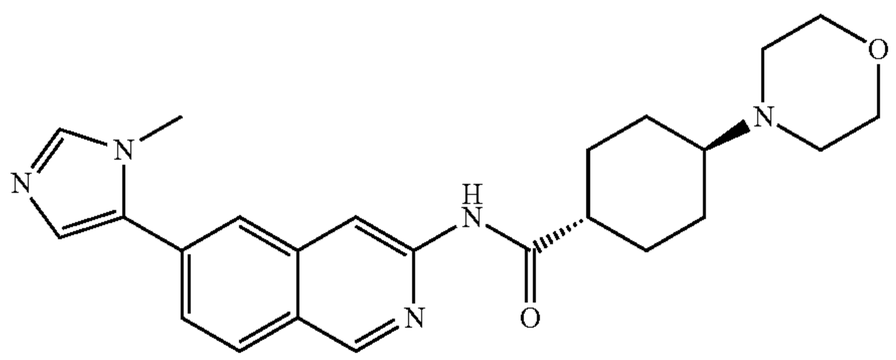

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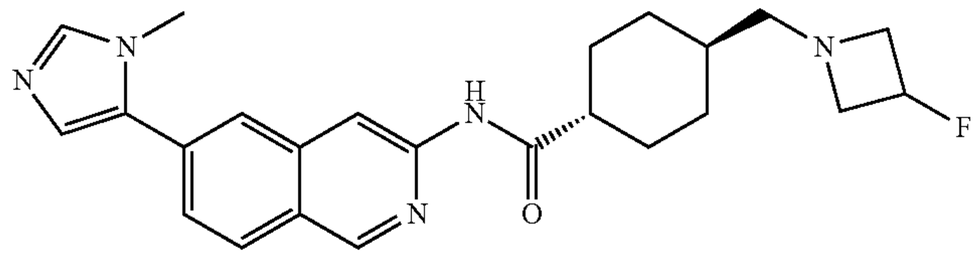

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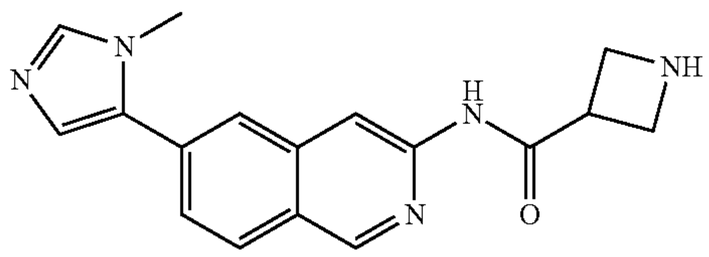

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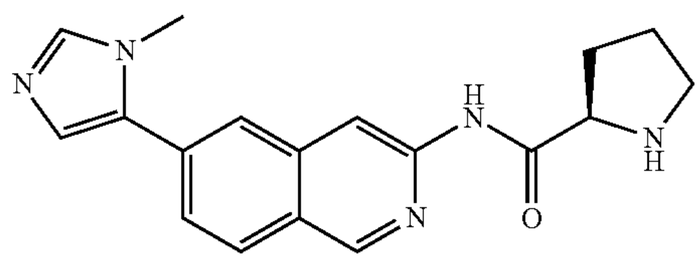

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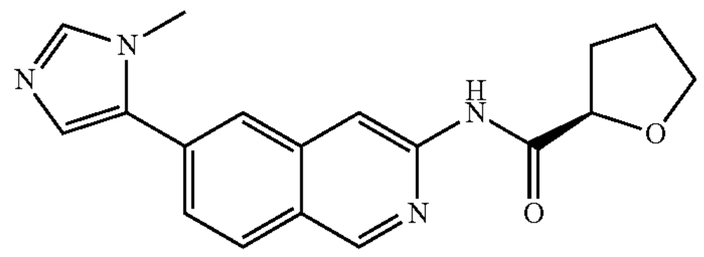
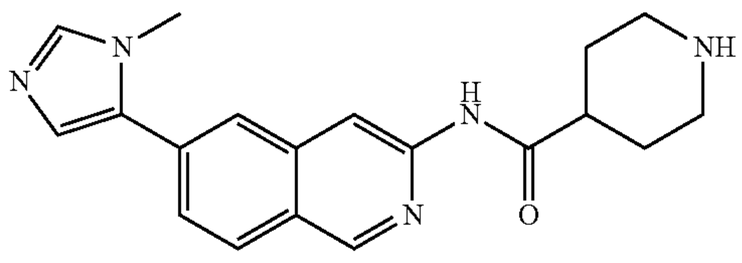
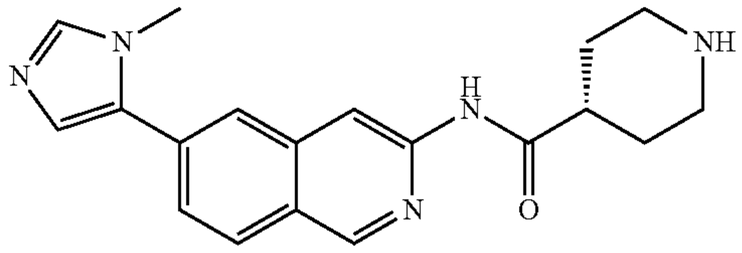
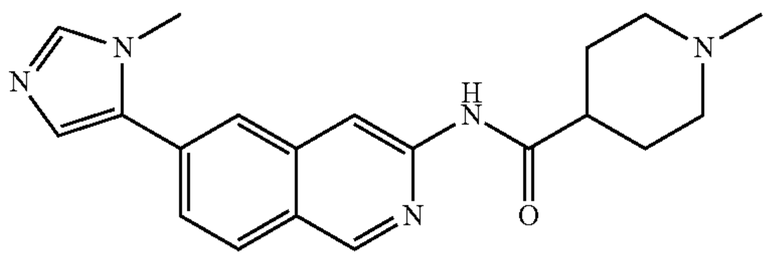
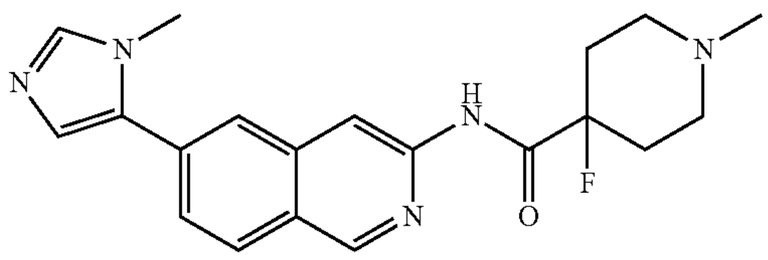
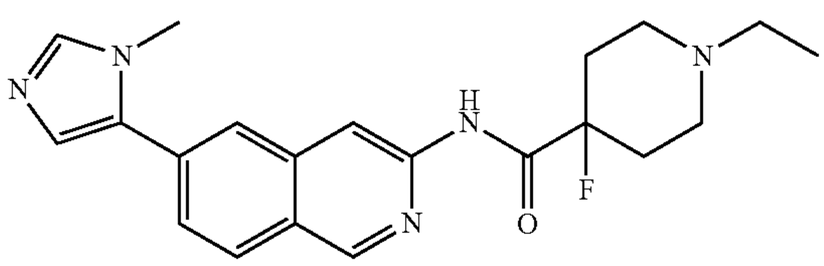
	537
	538
	539
	540
	541
	542
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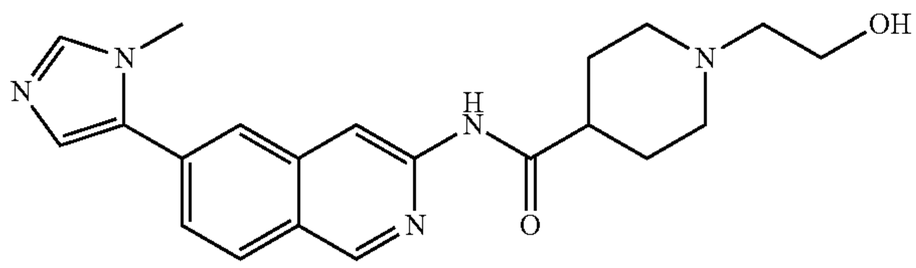
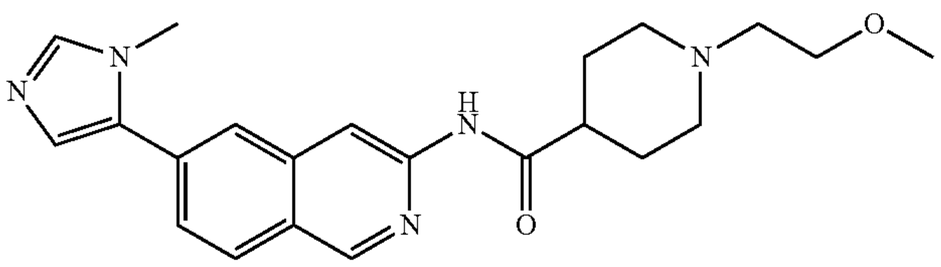
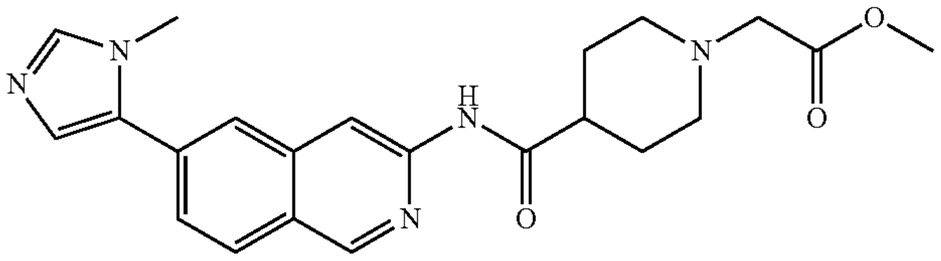
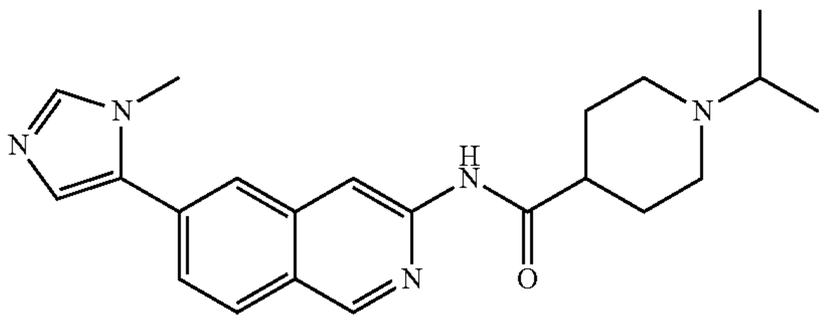
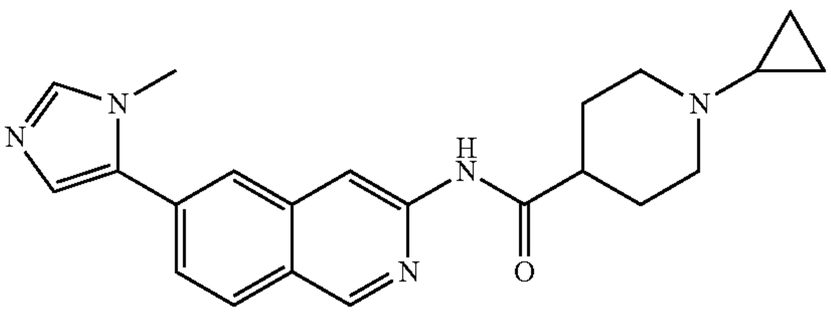
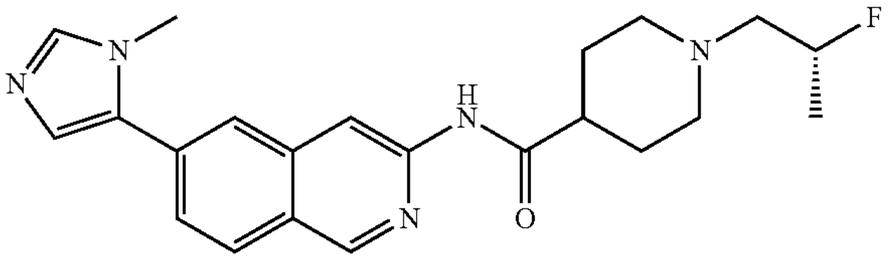
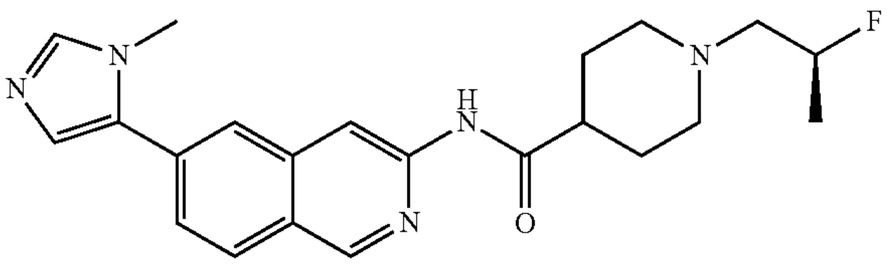
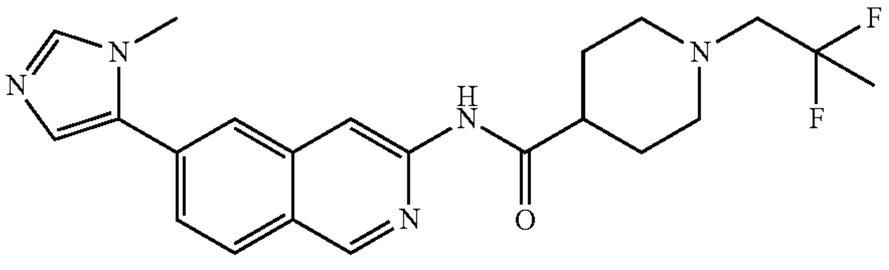
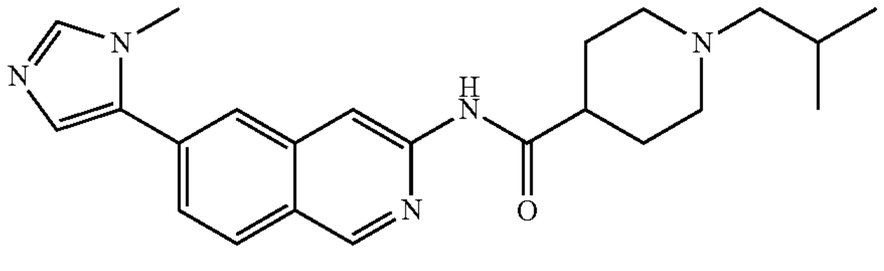
	546
	547
	548
	549
	550
	551
	552
	553
	554

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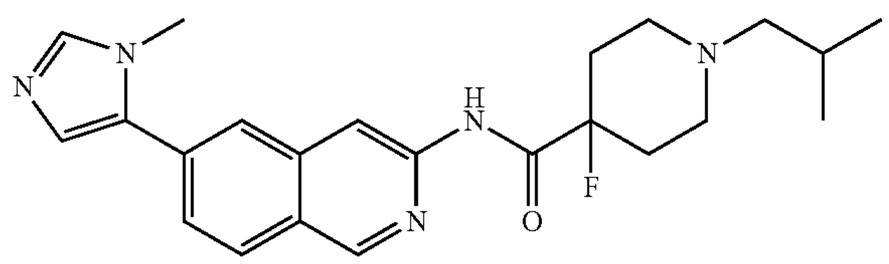
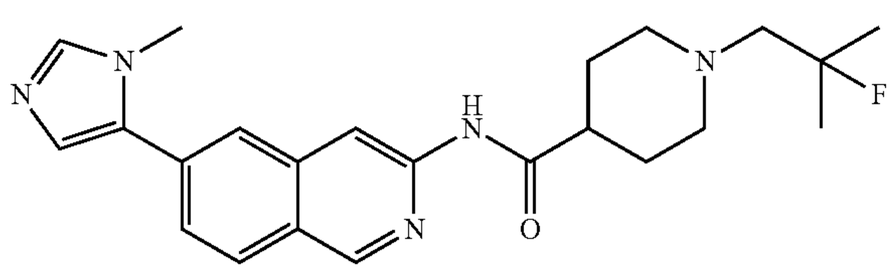
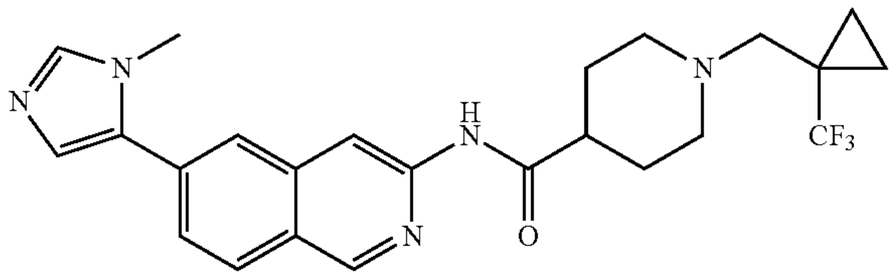
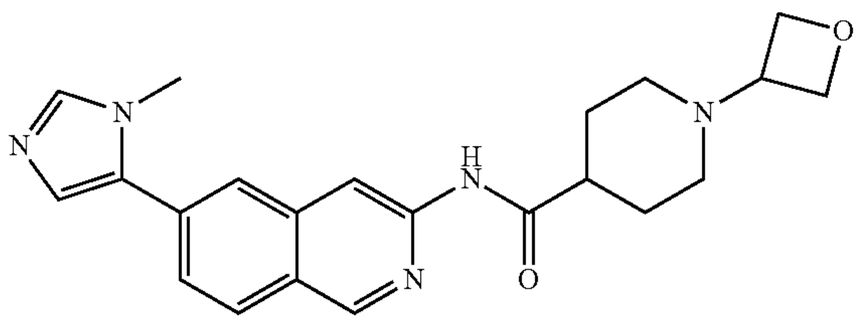
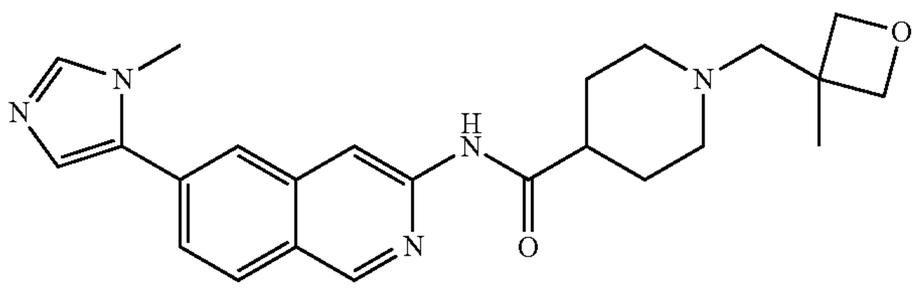
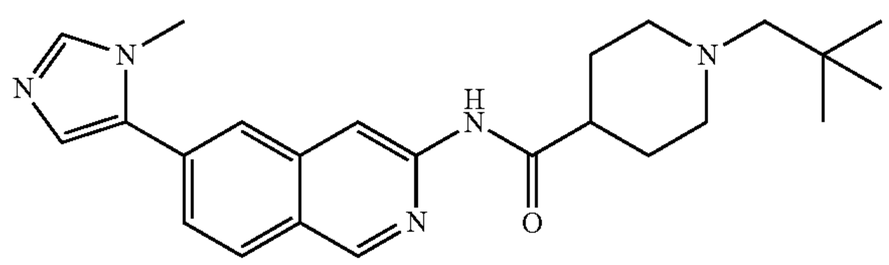
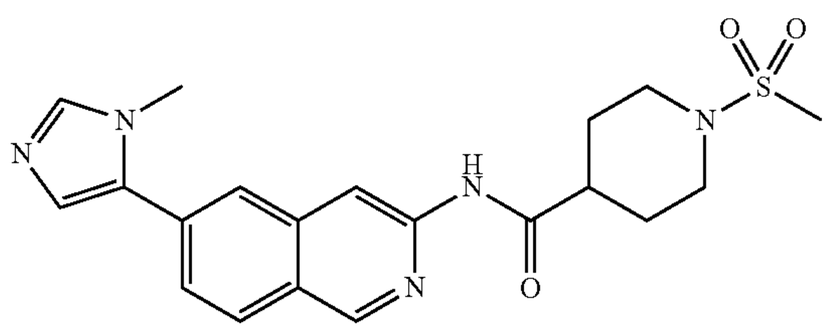
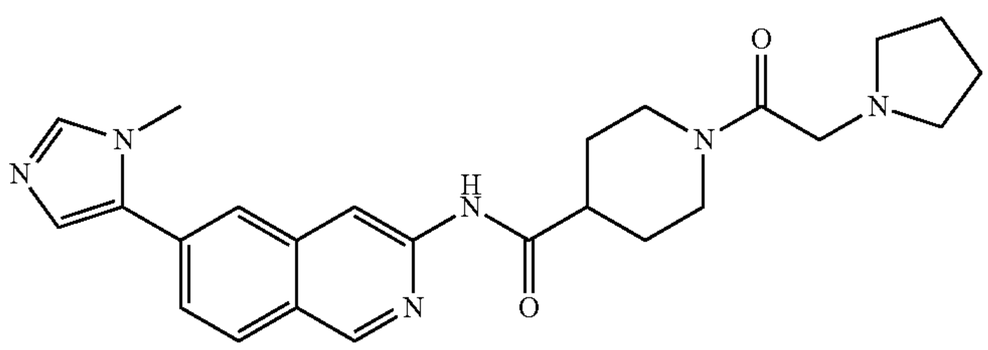
	555
	556
	557
	558
	559
	560
	561
	562

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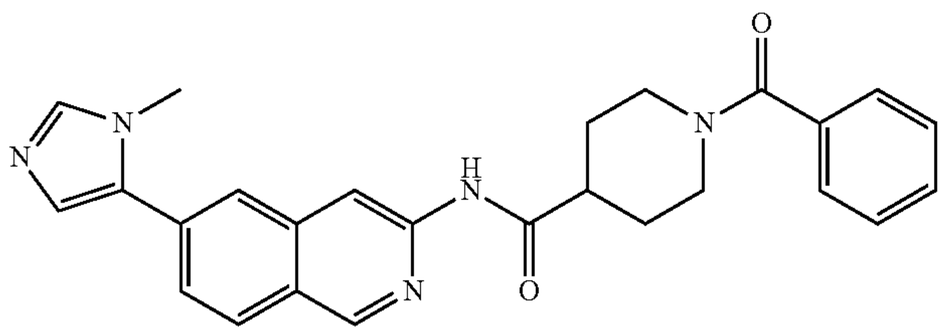

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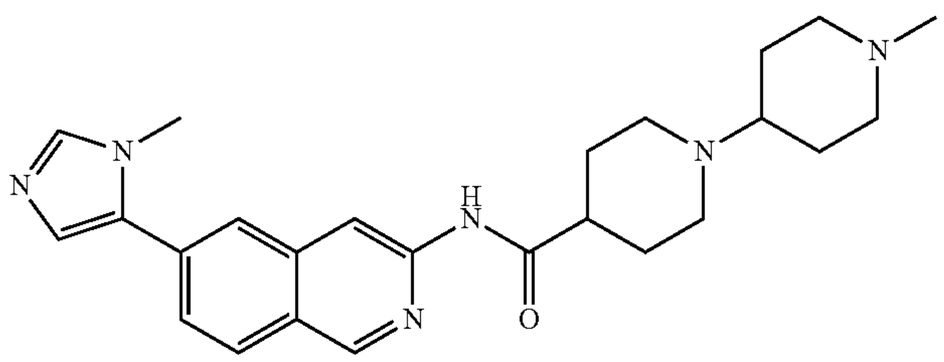

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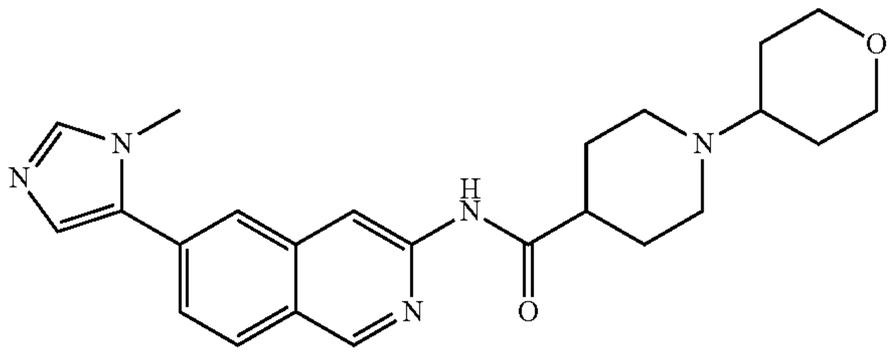

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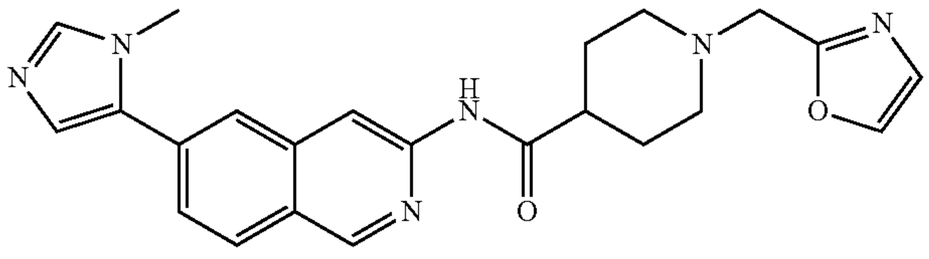

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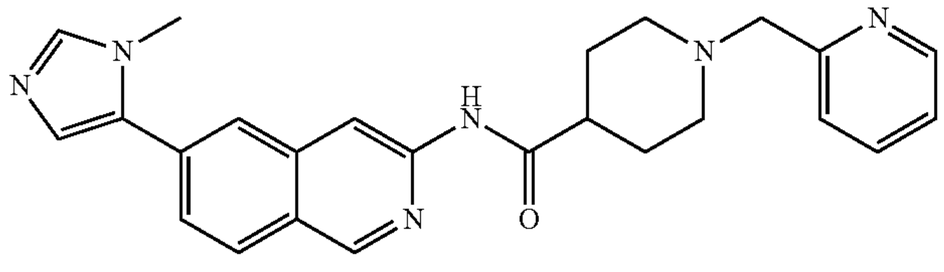

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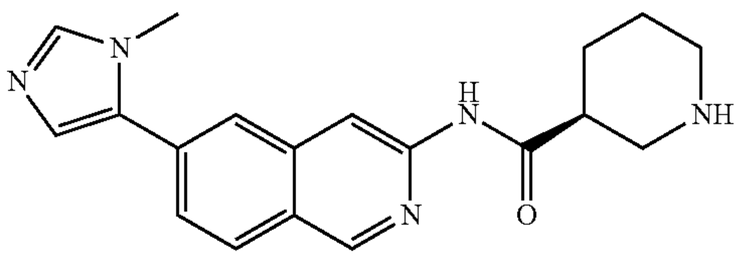

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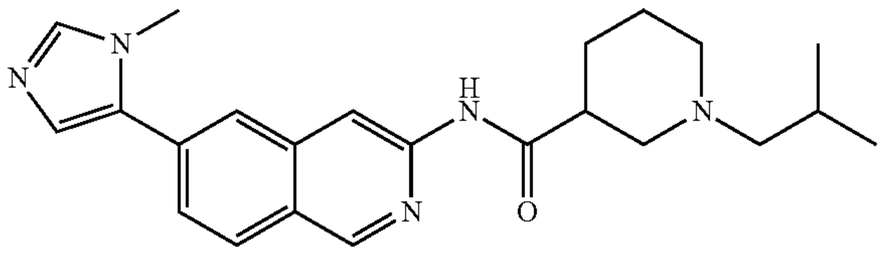

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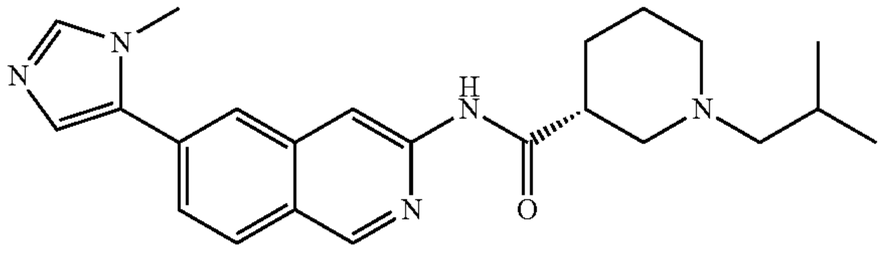

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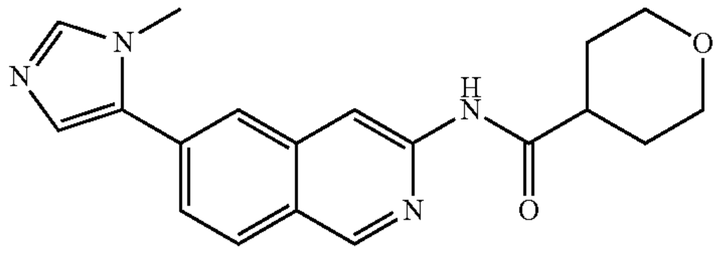
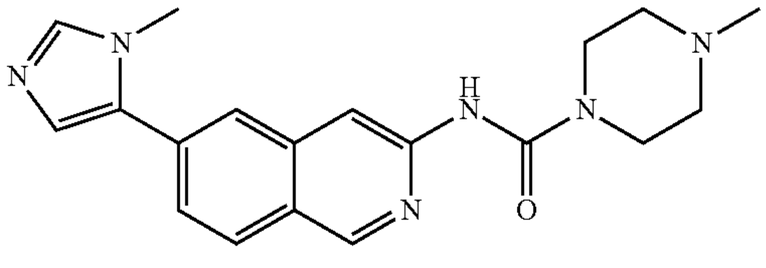
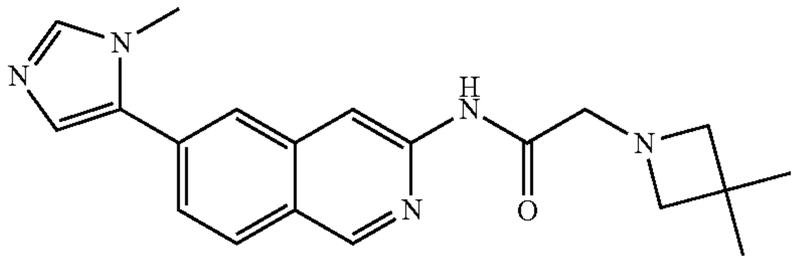
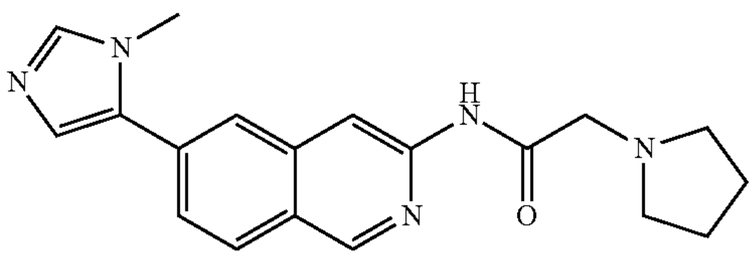
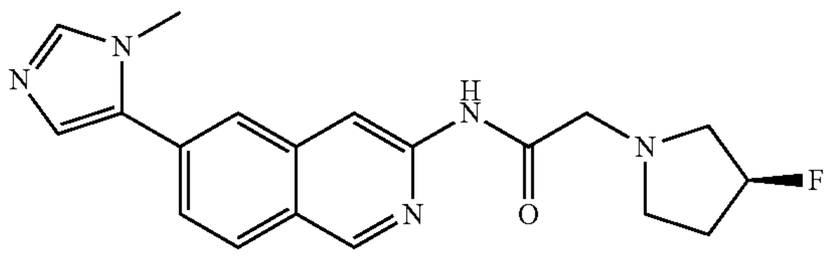
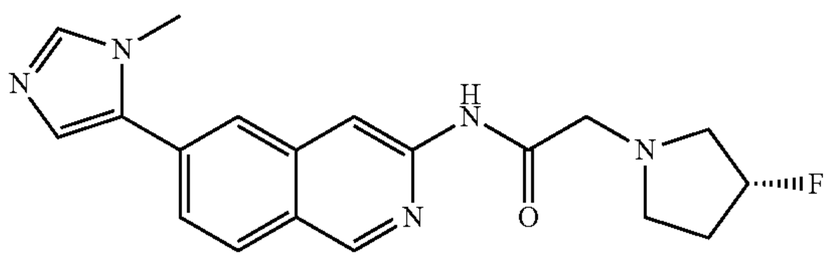
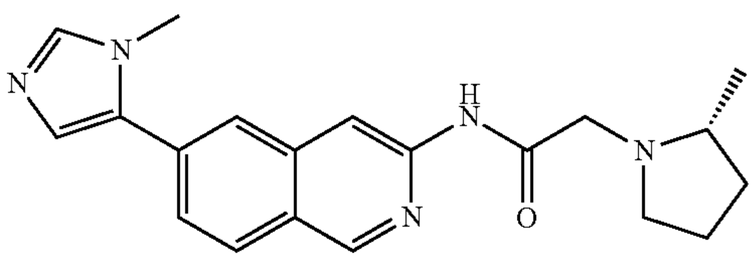
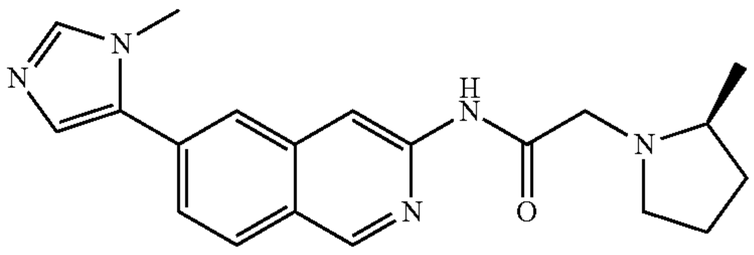
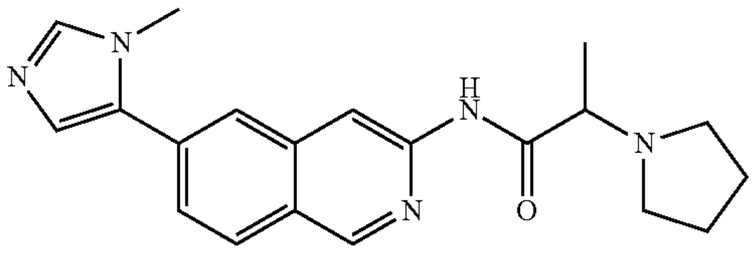
	571
	572
	573
	574
	575
	576
	577
	578
	579

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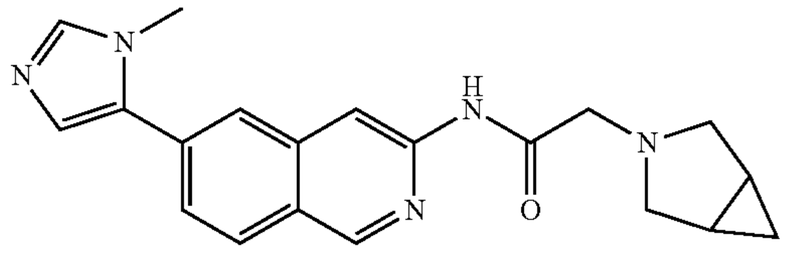
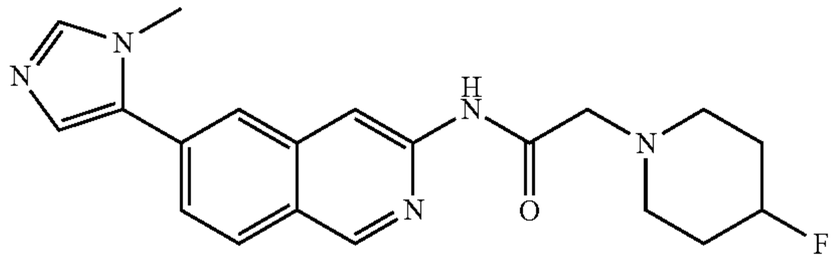
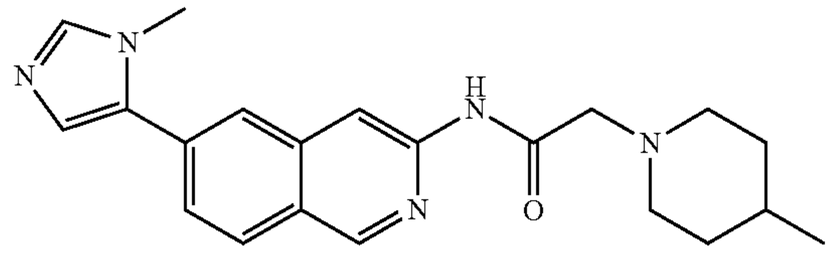
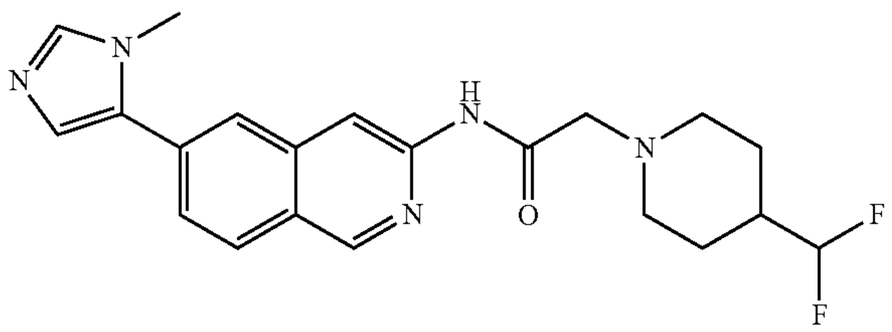
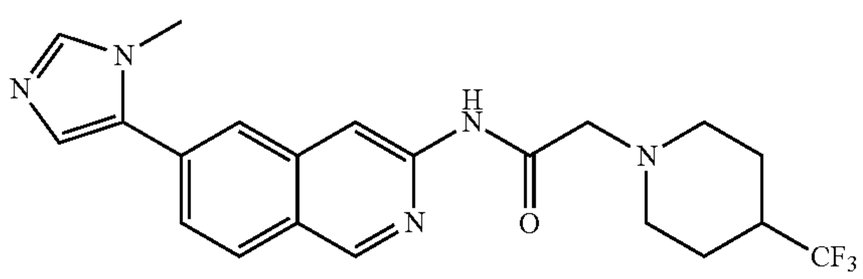
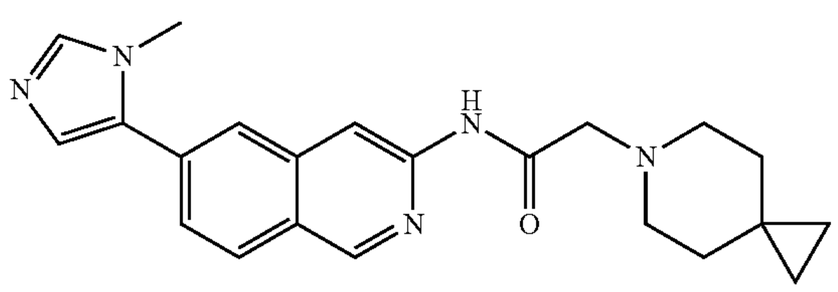
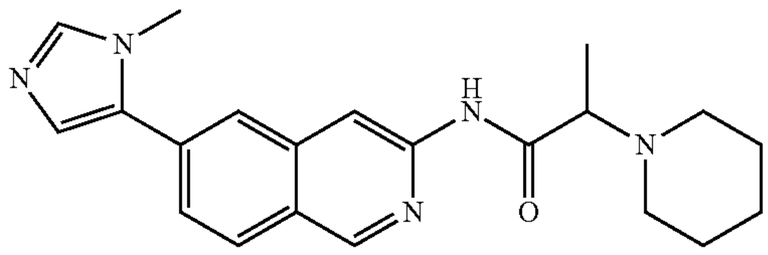
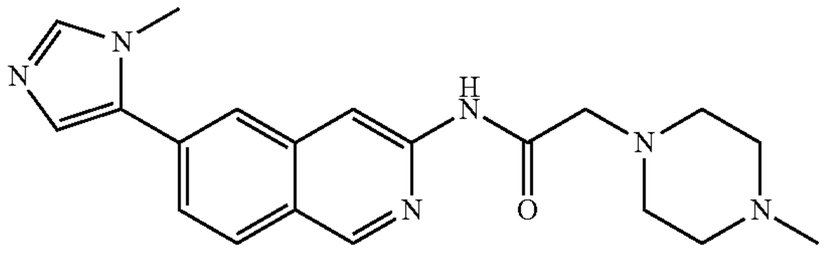
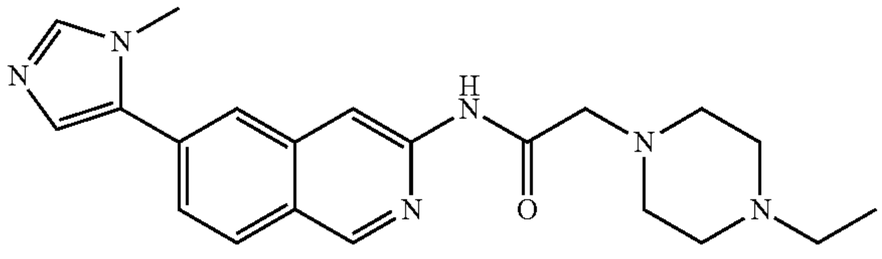
	580
	581
	582
	583
	584
	585
	586
	587
	588

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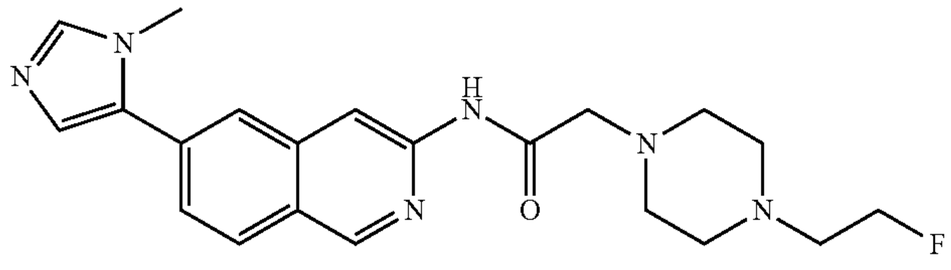
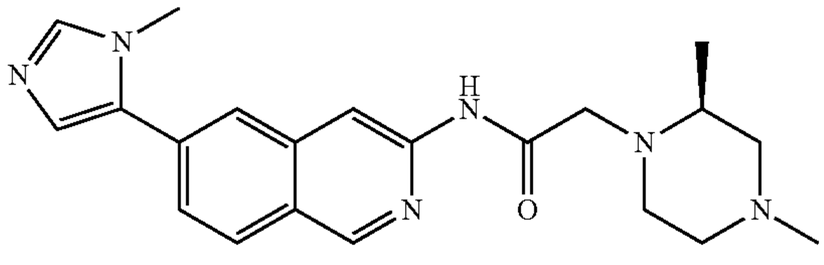
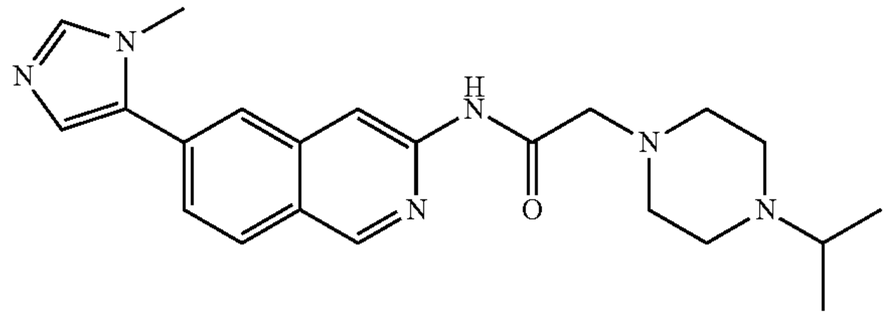
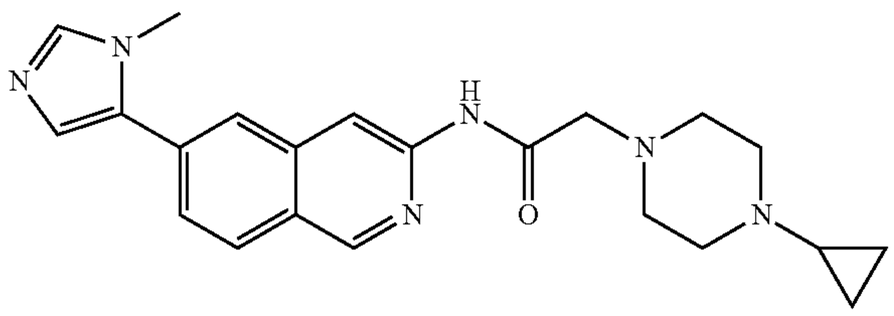
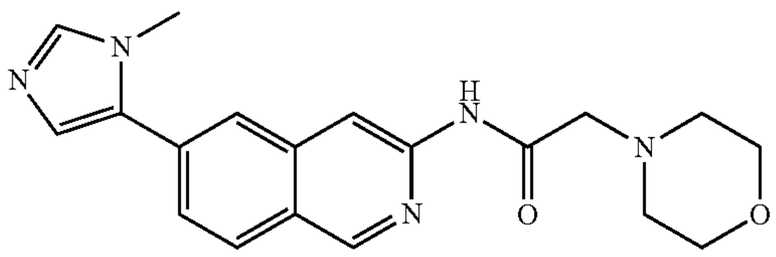
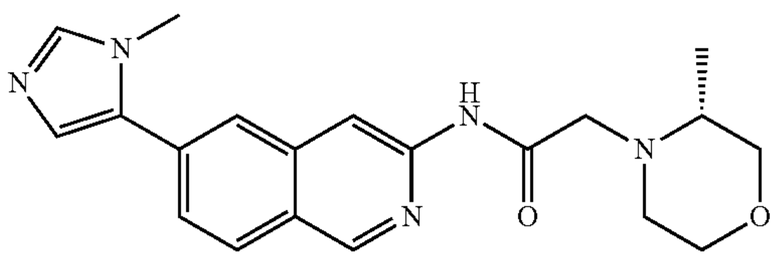
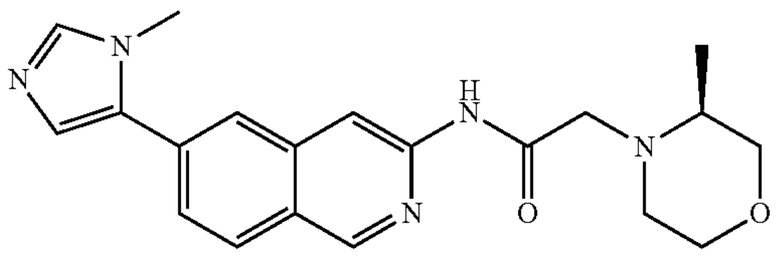
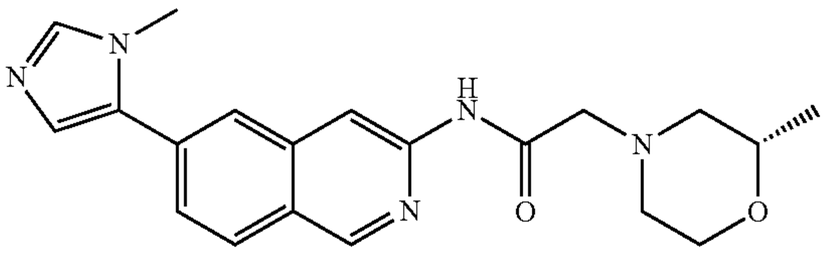
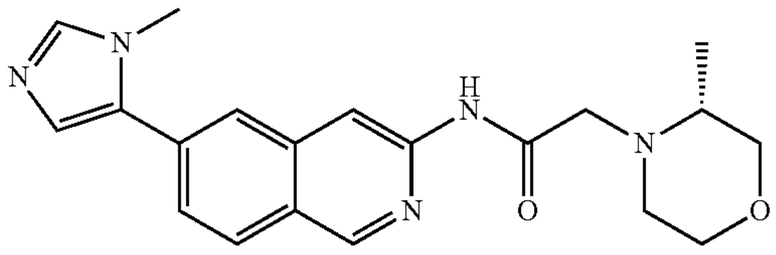
	589
	590
	591
	592
	593
	594
	595
	596
	597

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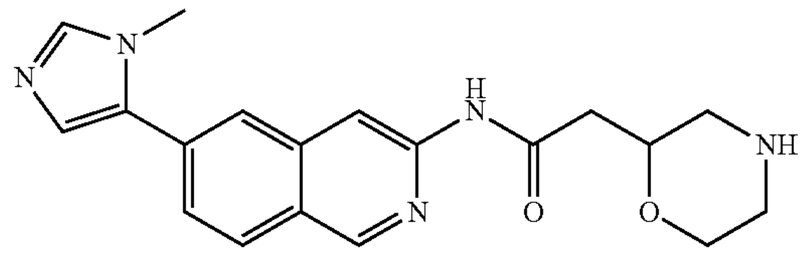
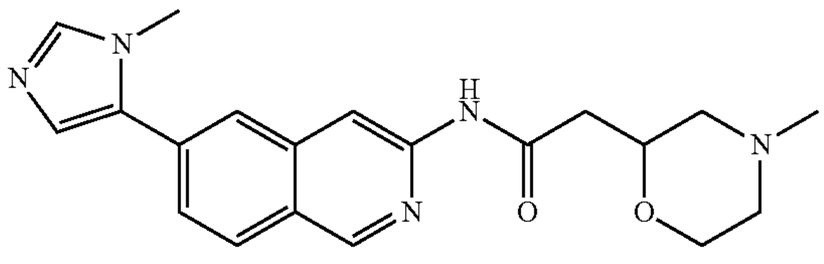
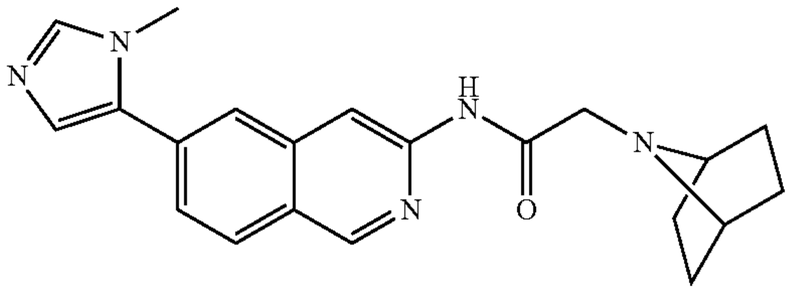
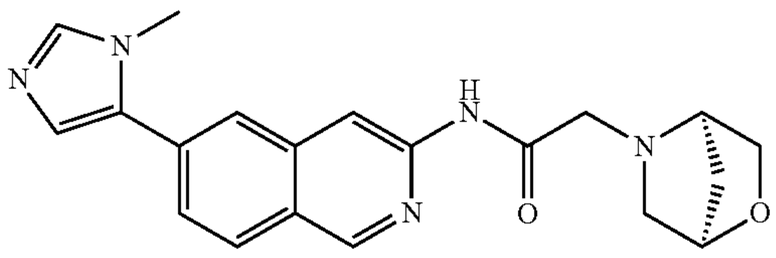
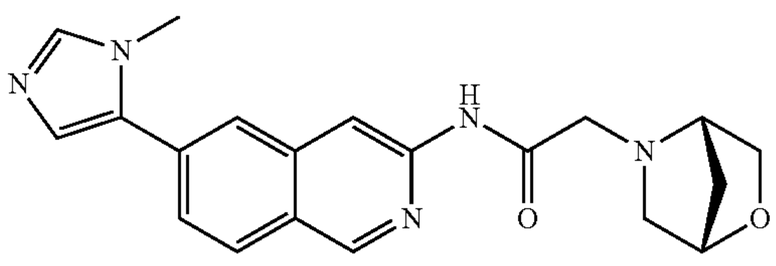
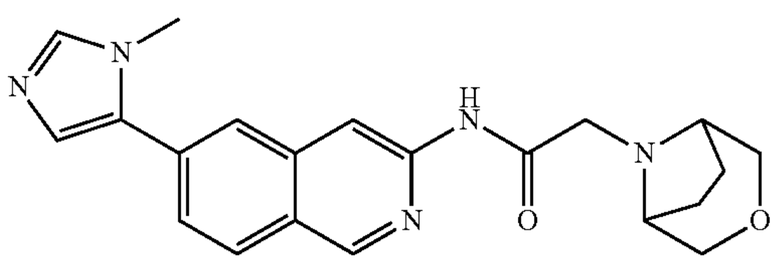
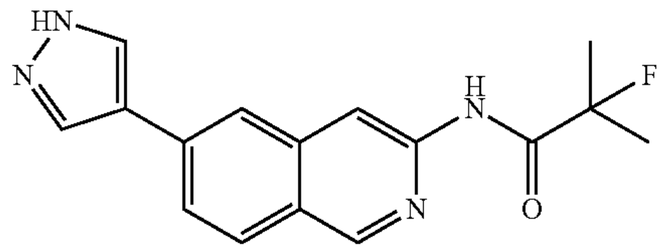
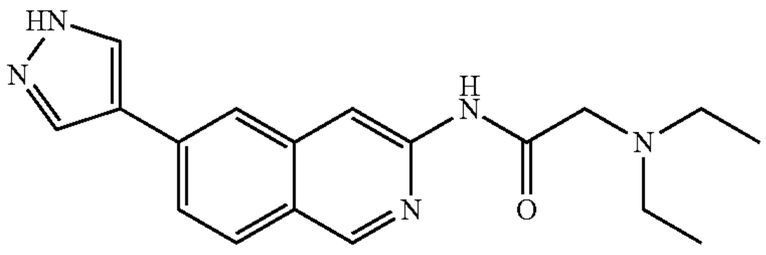
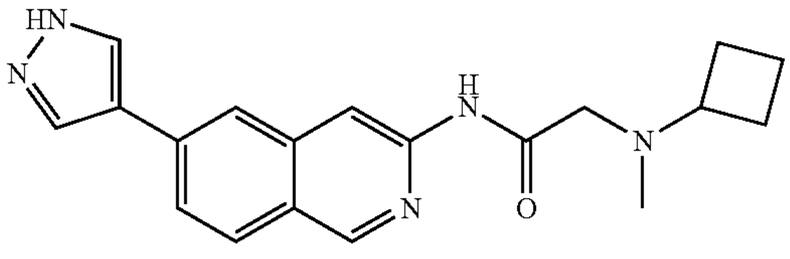
	598
	599
	600
	601
	602
	603
	604
	605
	606

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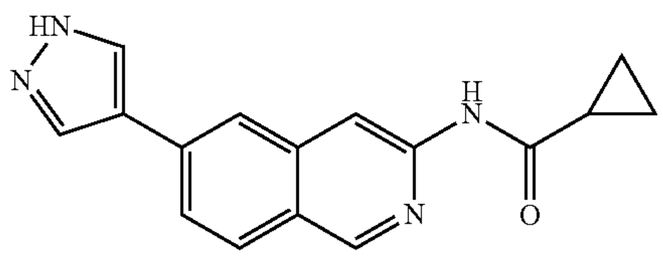
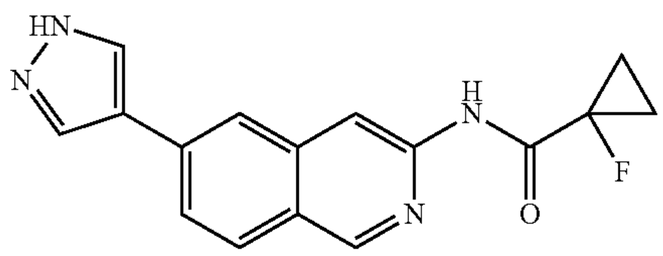
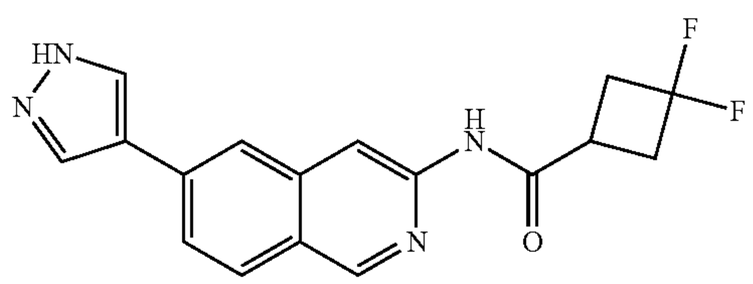
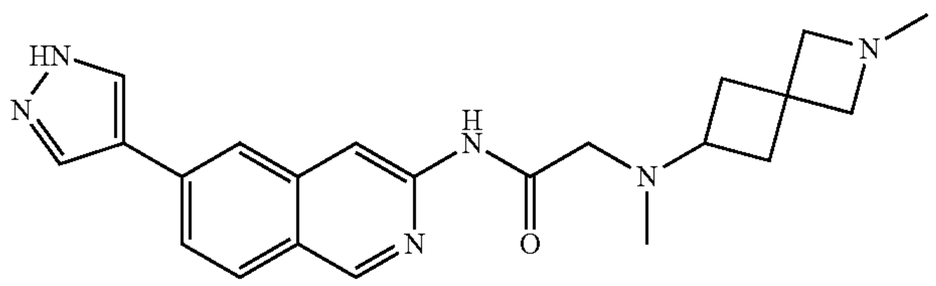
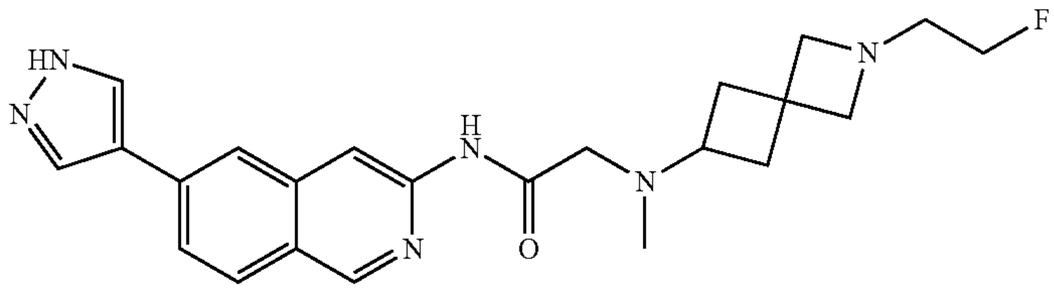
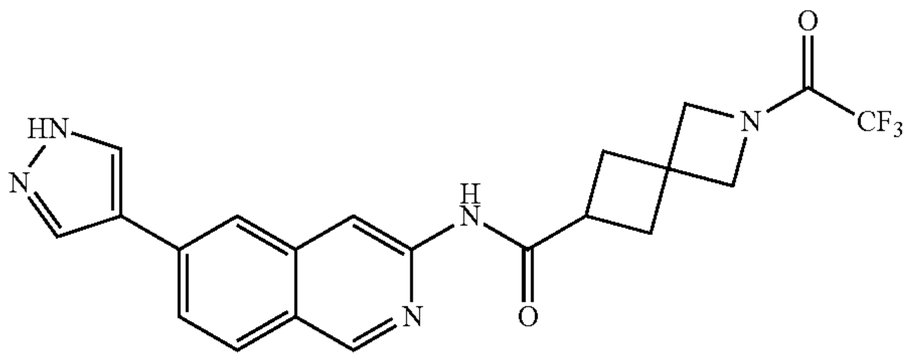
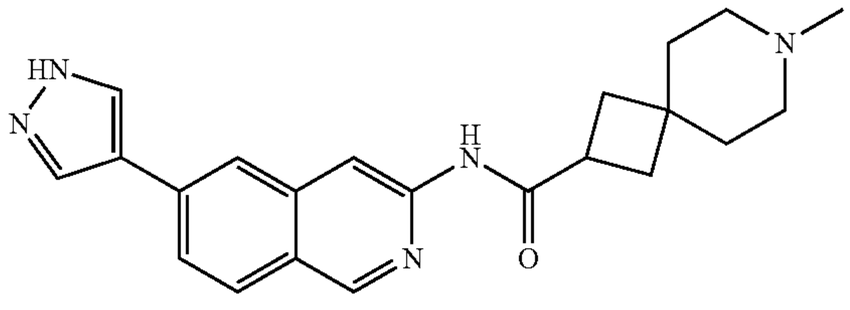
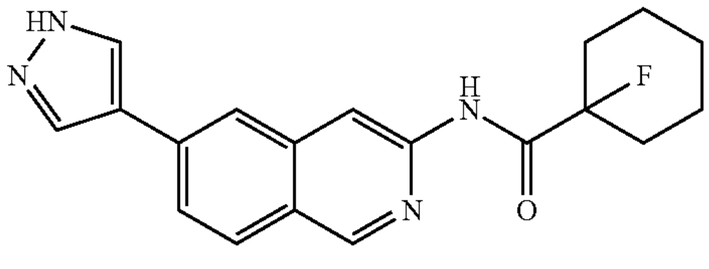
	607
	608
	609
	610
	611
	612
	613
	614

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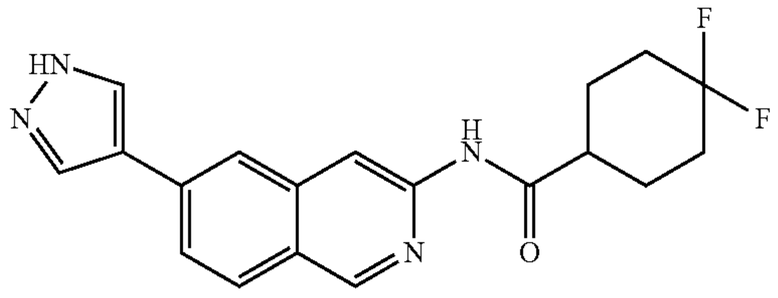
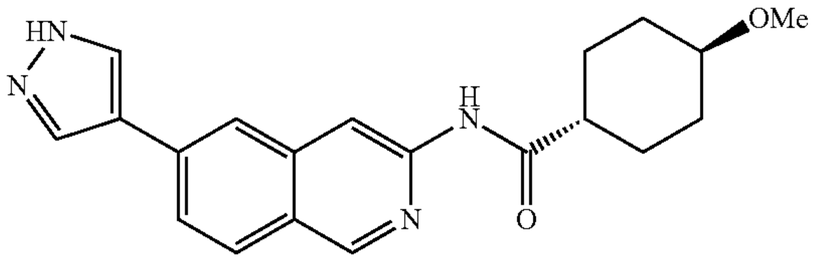
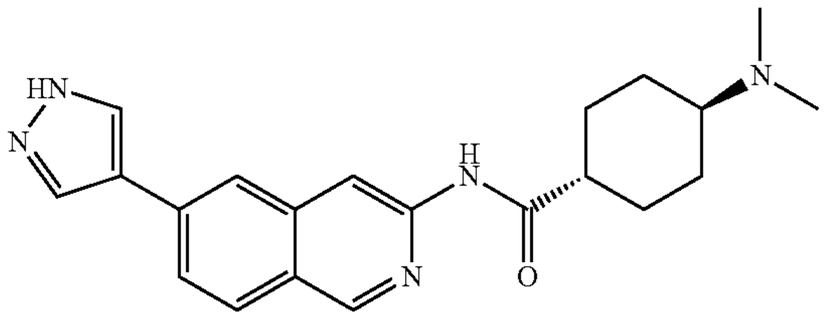
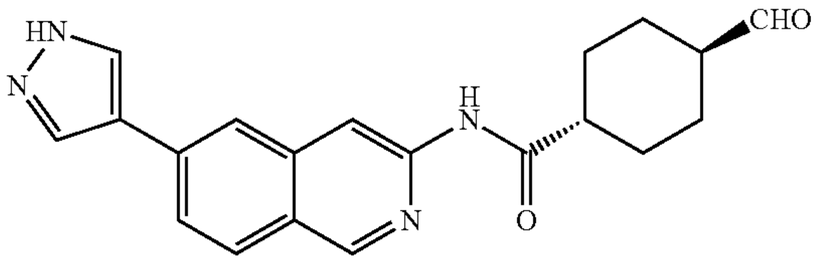
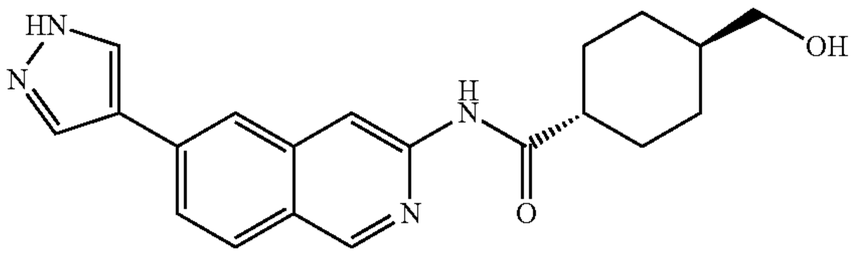
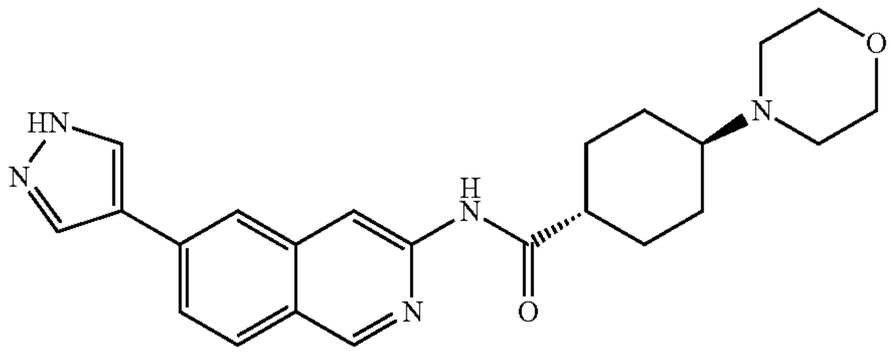
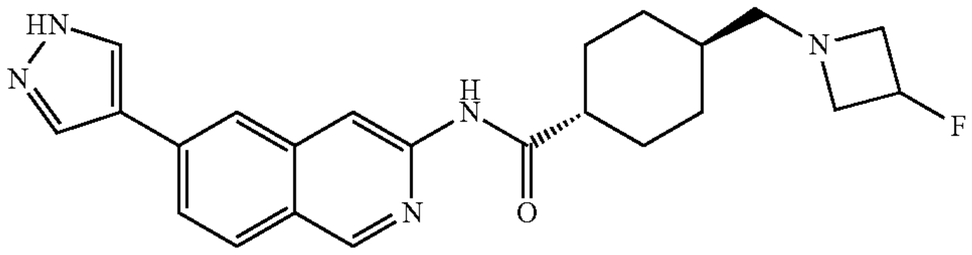
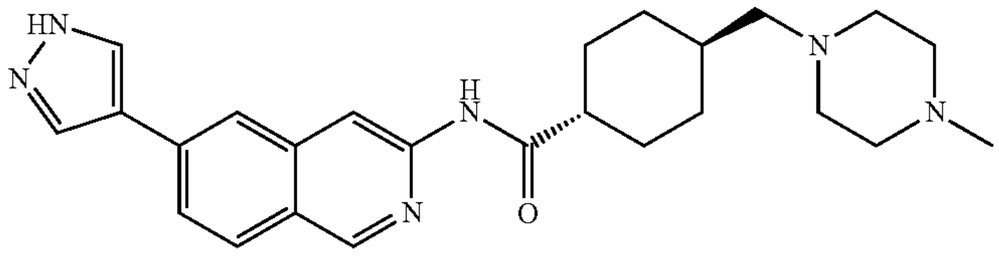
	615
	616
	617
	618
	619
	620
	621
	622

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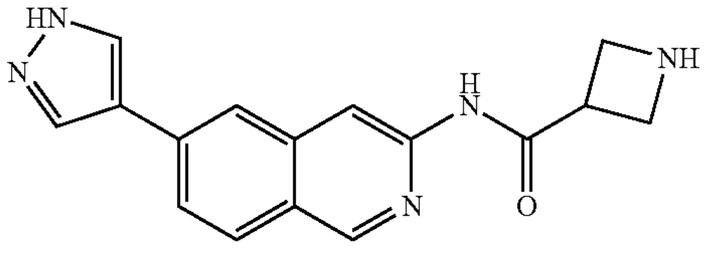
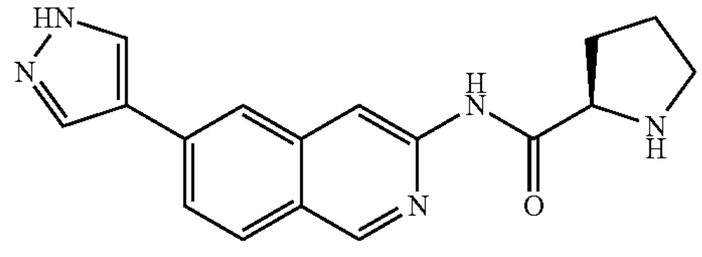
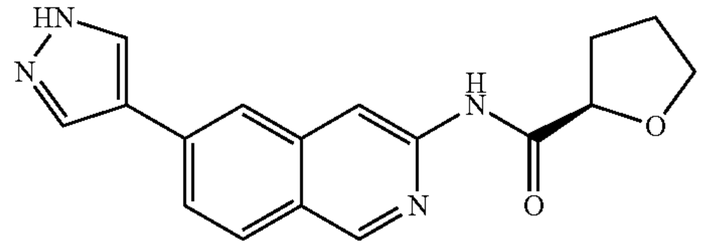
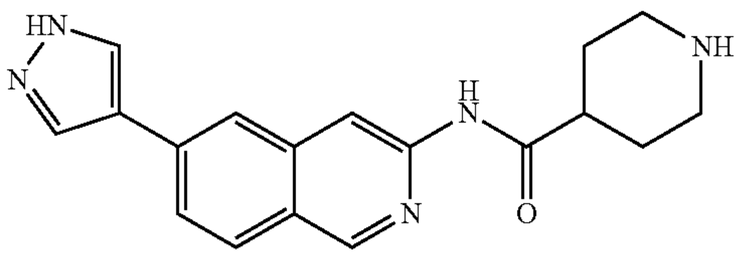
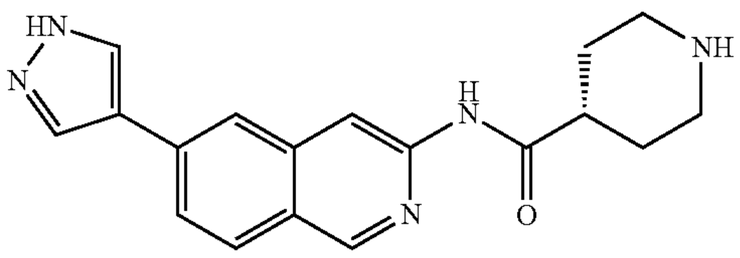
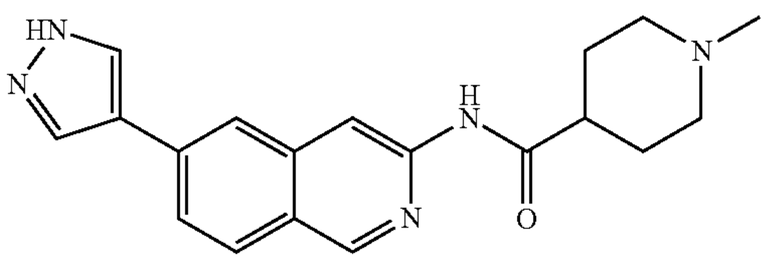
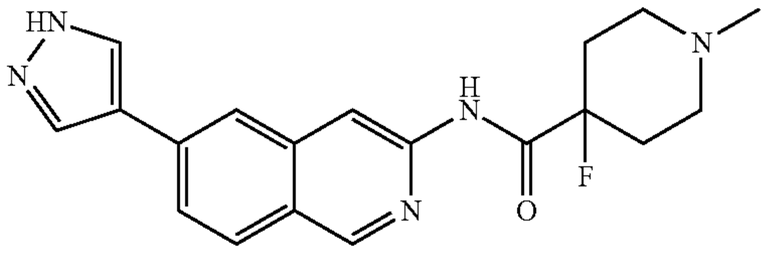
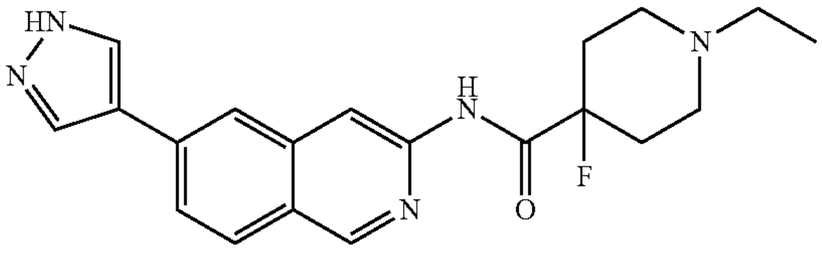
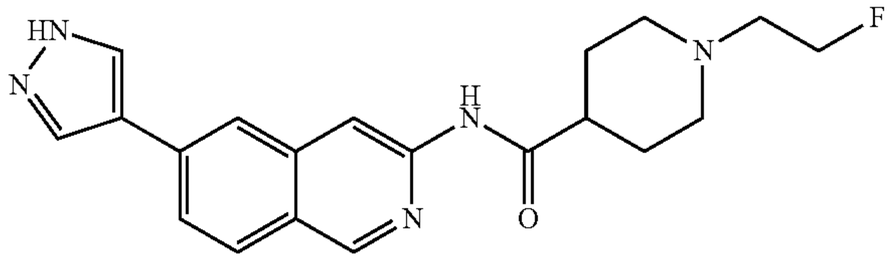
	623
	624
	625
	626
	627
	628
	629
	630
	631

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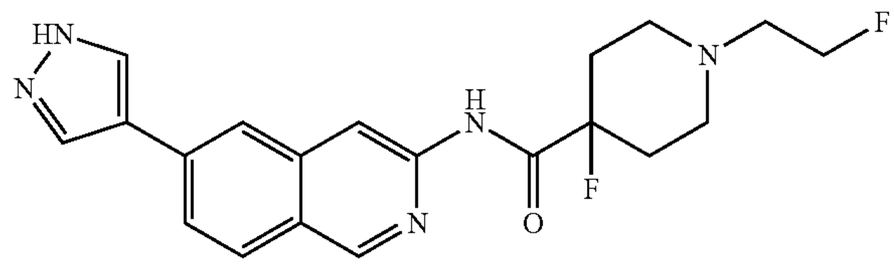
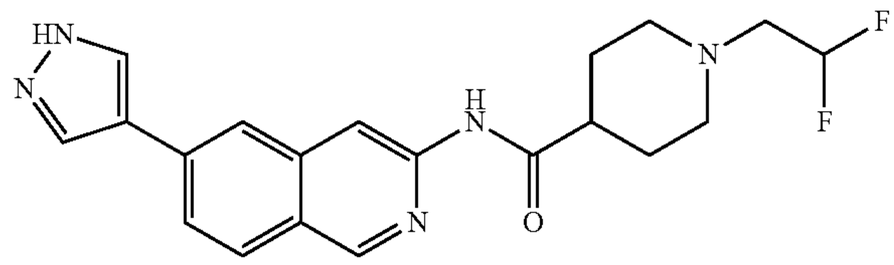
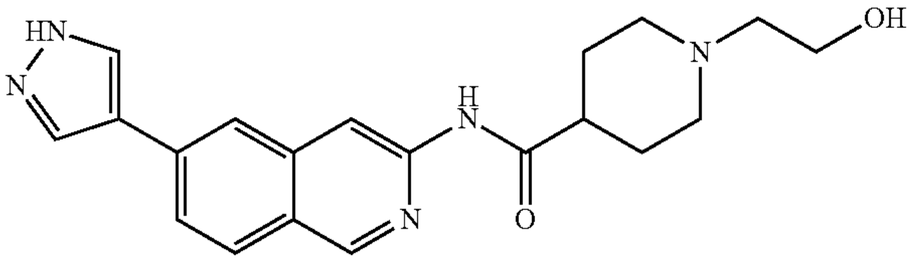
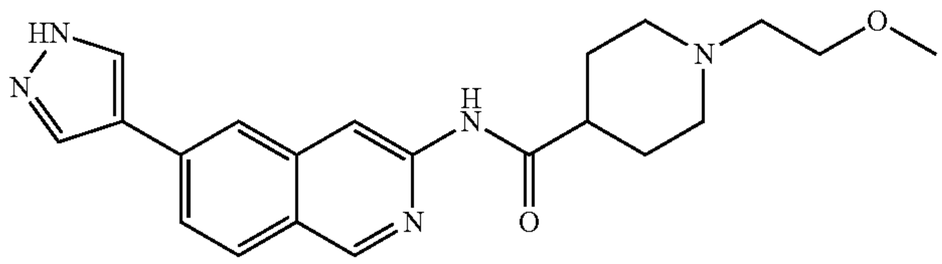
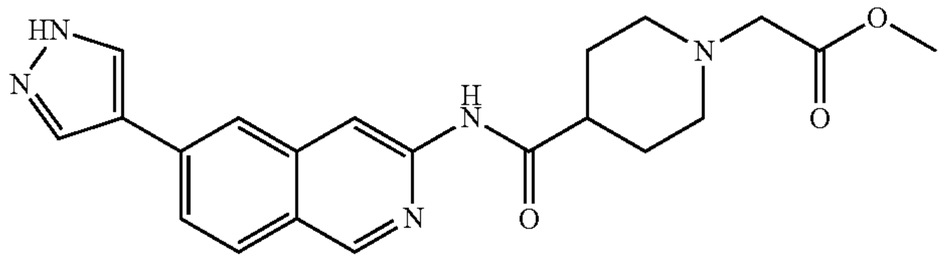
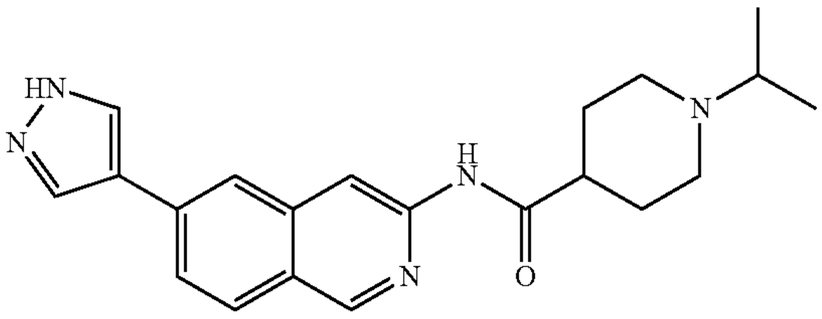
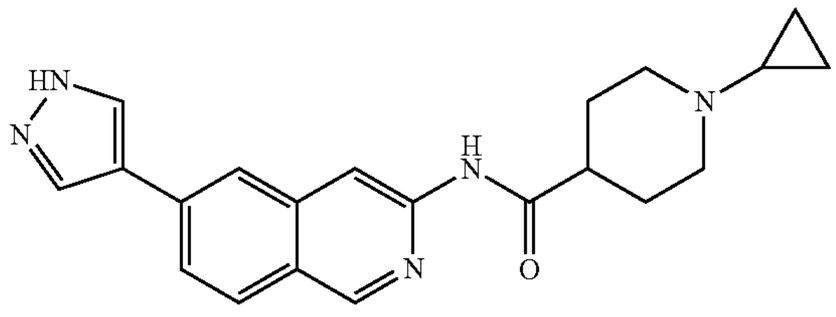
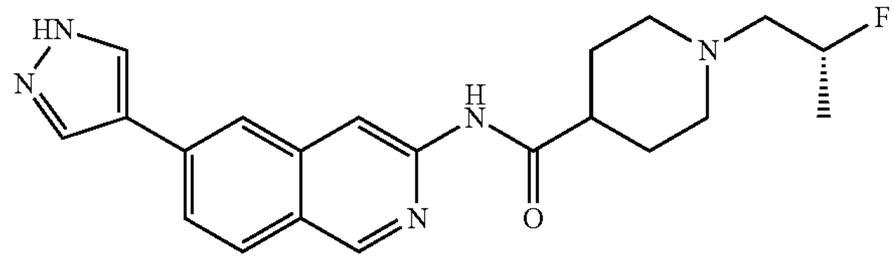
	632
	633
	634
	635
	636
	637
	638
	639

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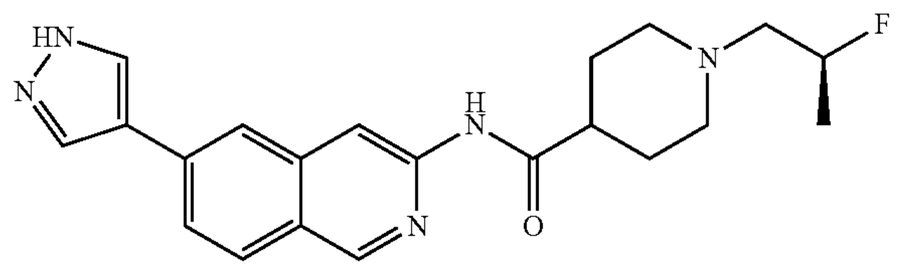
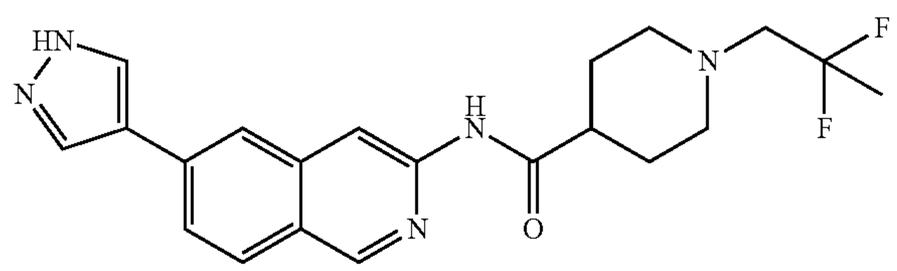
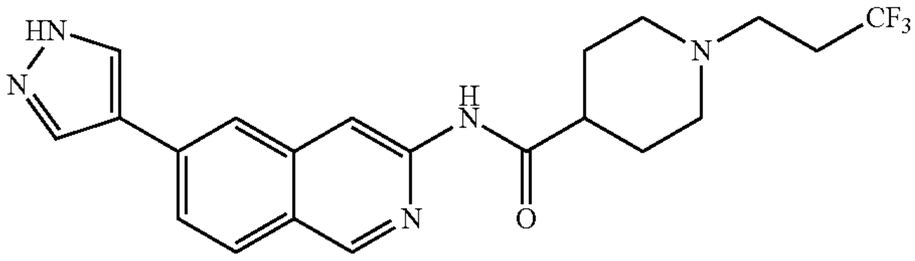
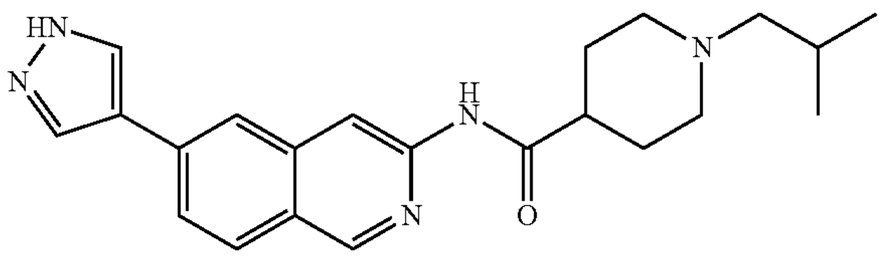
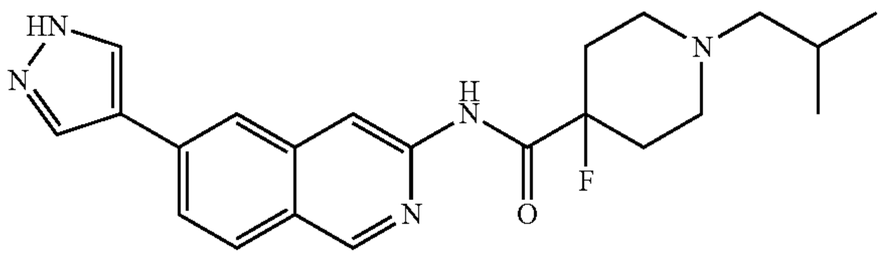
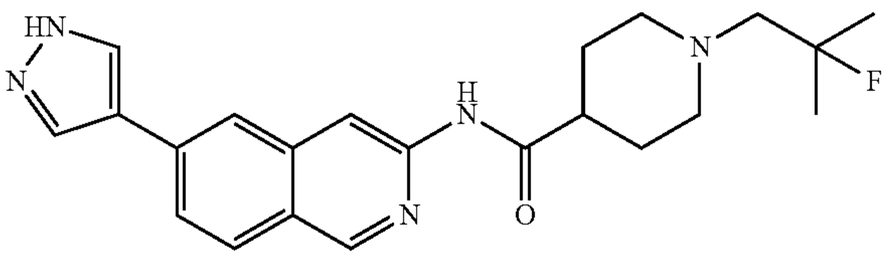
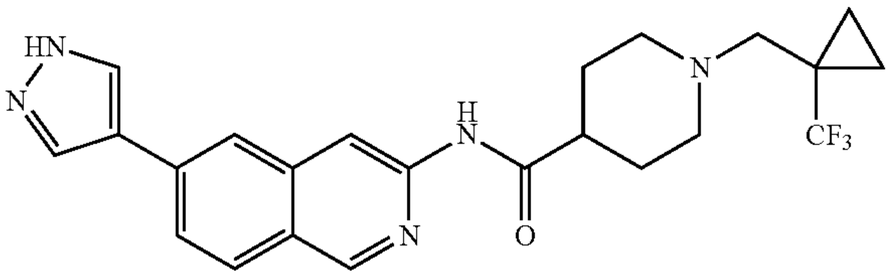
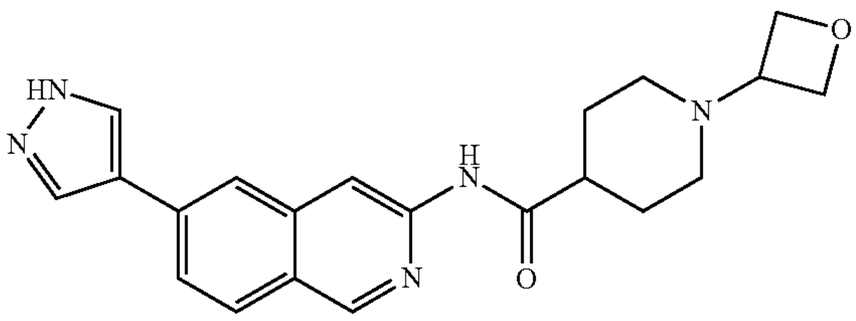
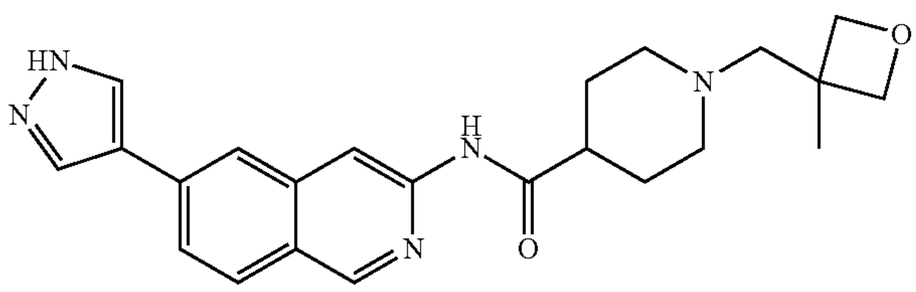
	640
	641
	642
	643
	644
	645
	646
	647
	648

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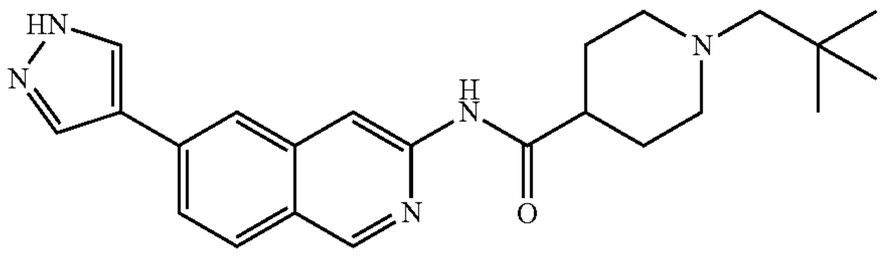

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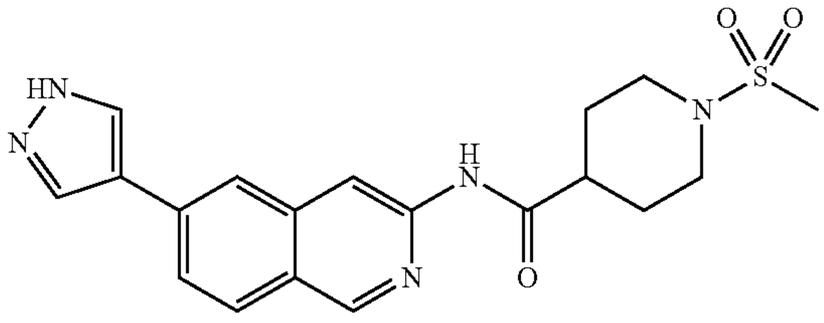

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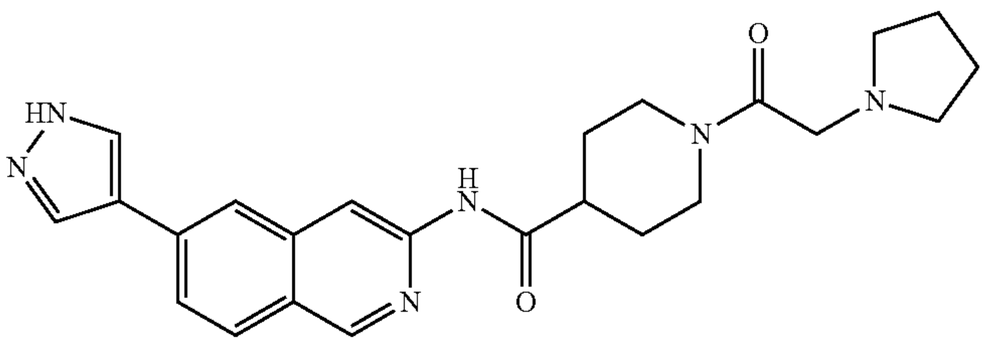

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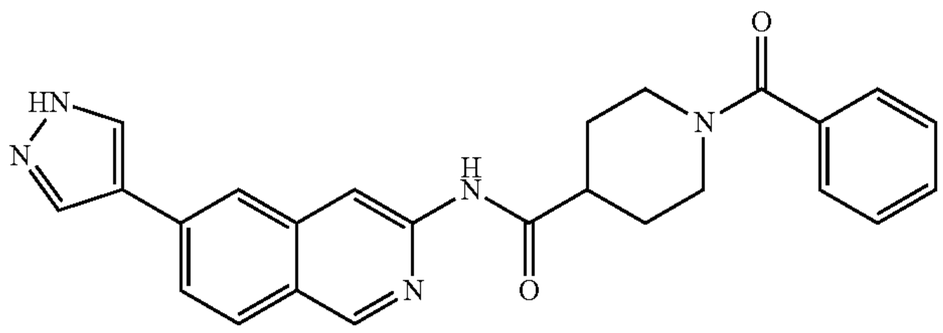

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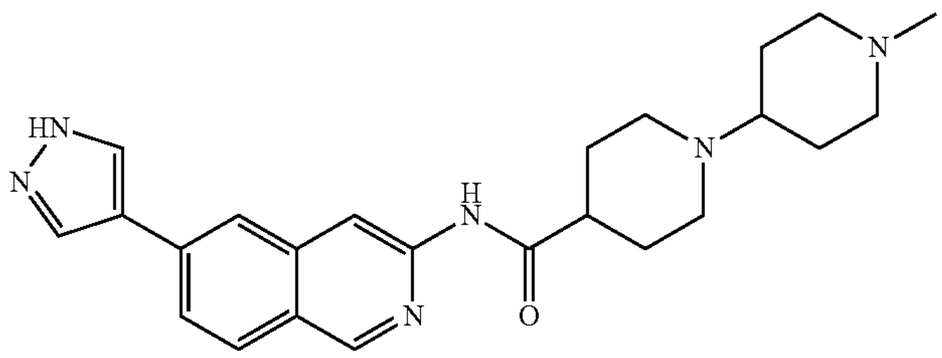

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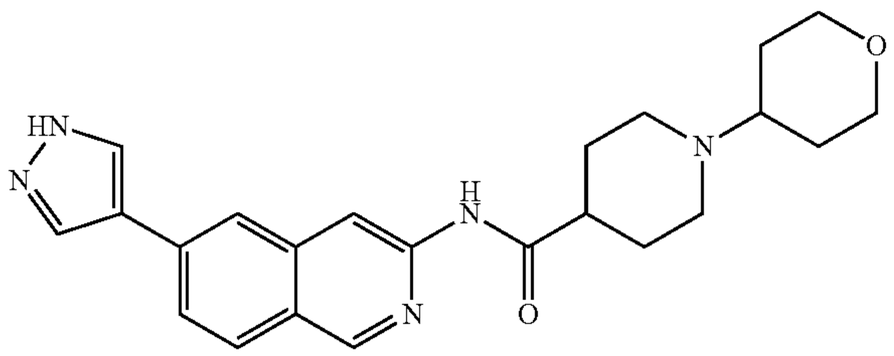

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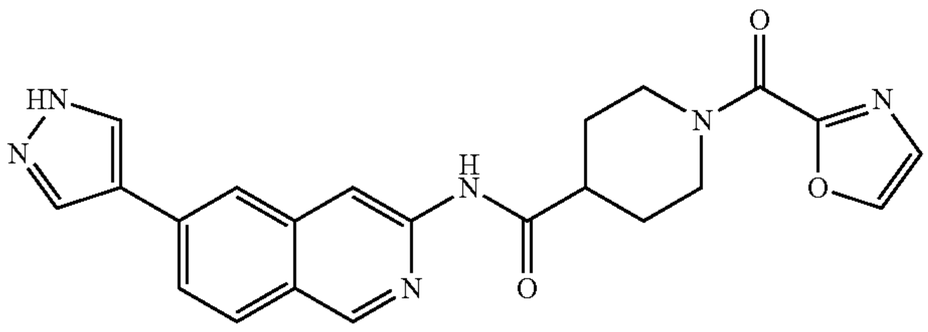

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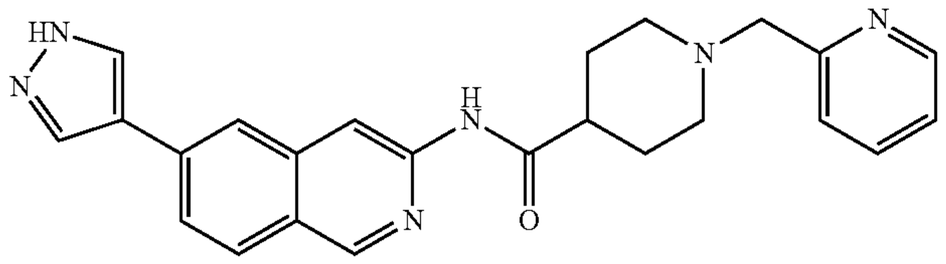
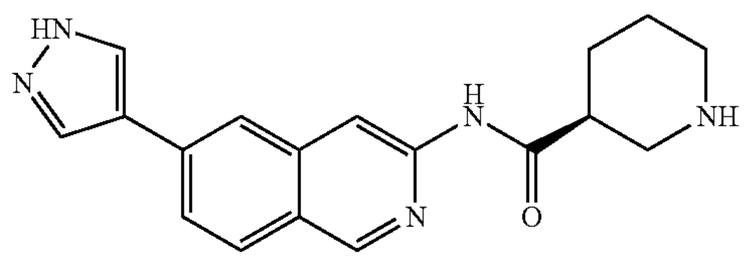
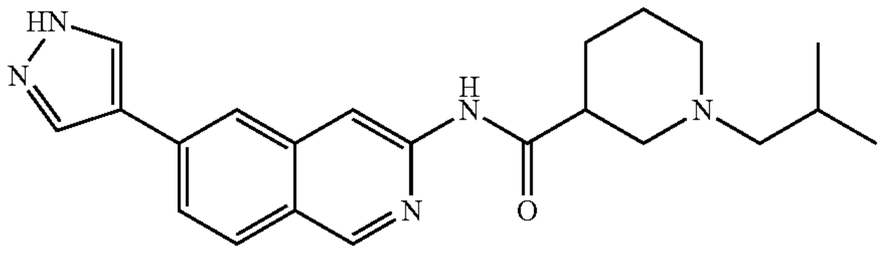
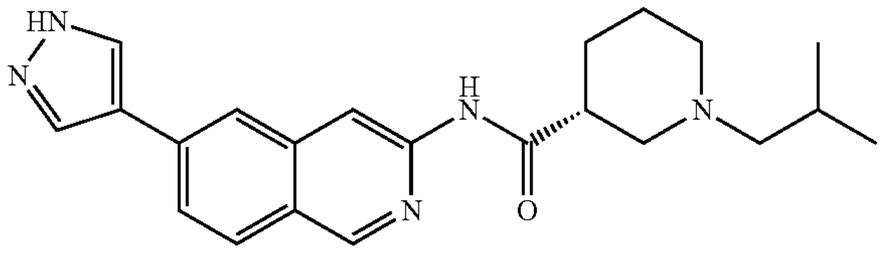
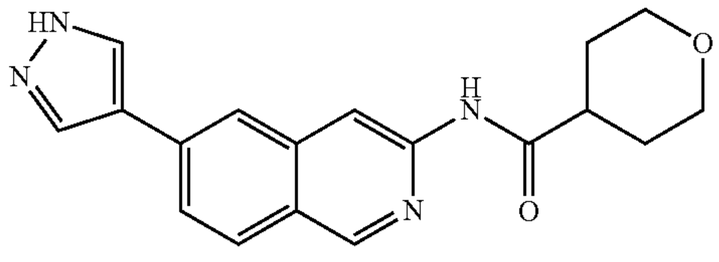
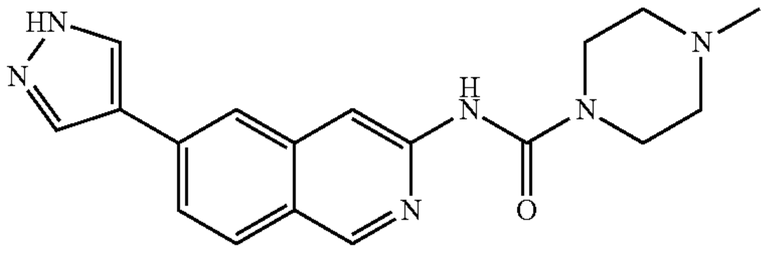
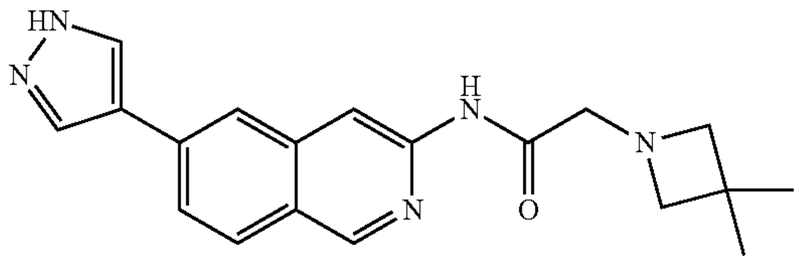
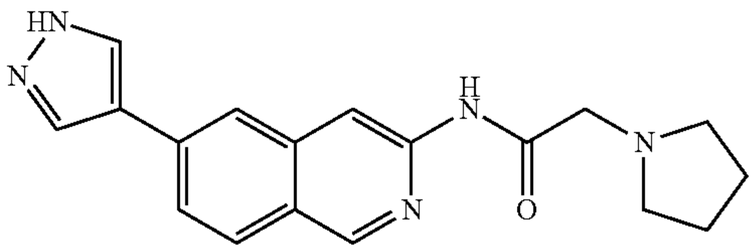
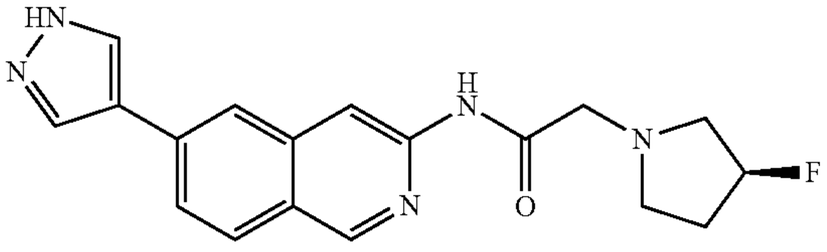
	656
	657
	658
	659
	660
	661
	662
	663
	664

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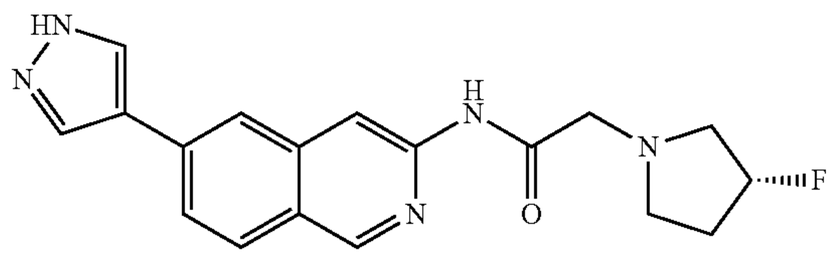
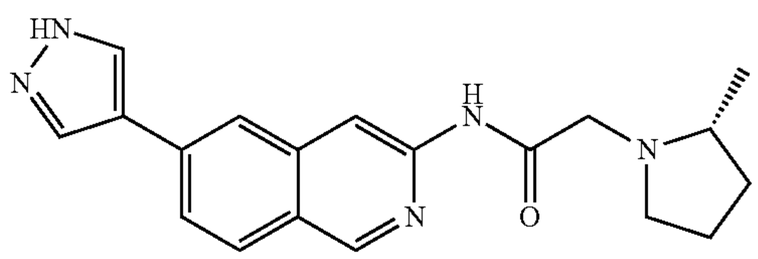
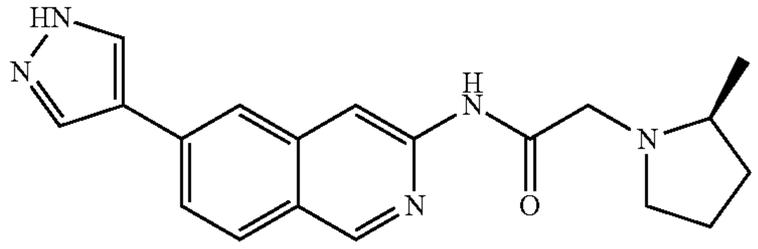
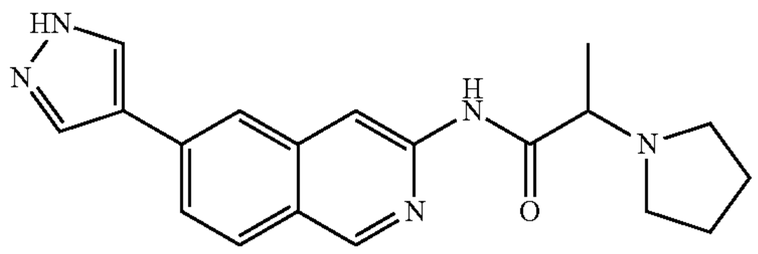
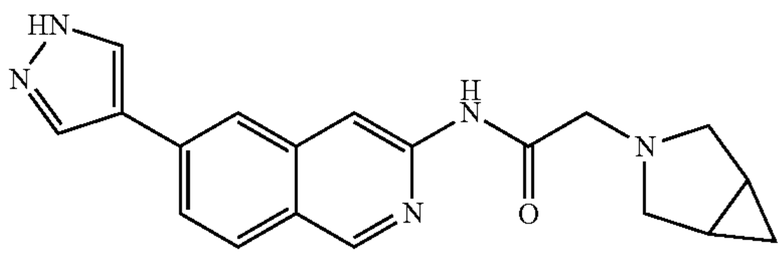
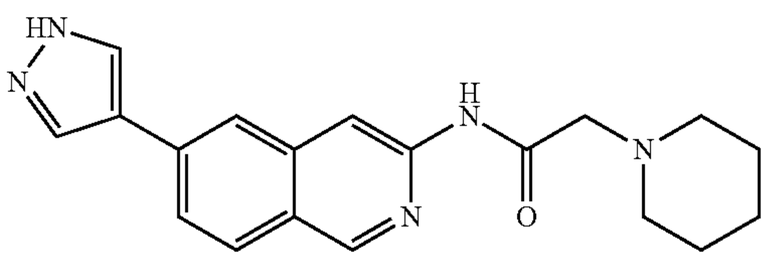
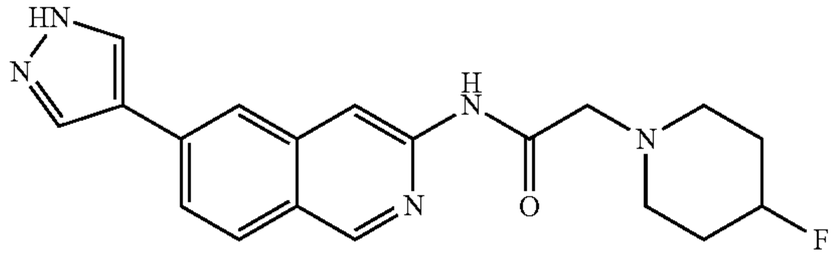
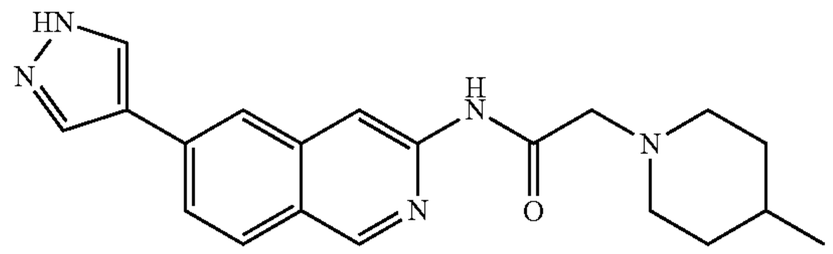
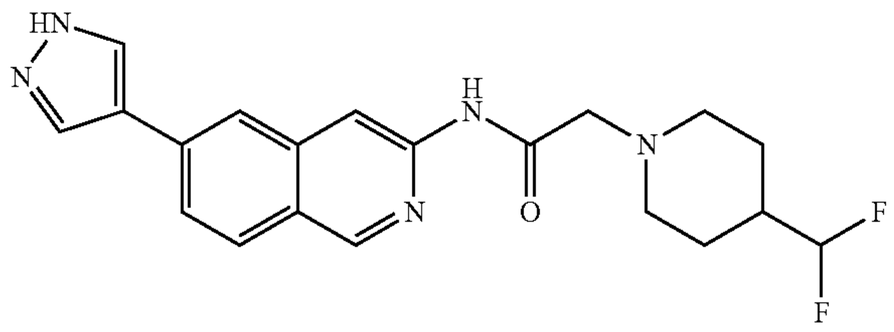
	665
	666
	667
	668
	669
	670
	671
	672
	673

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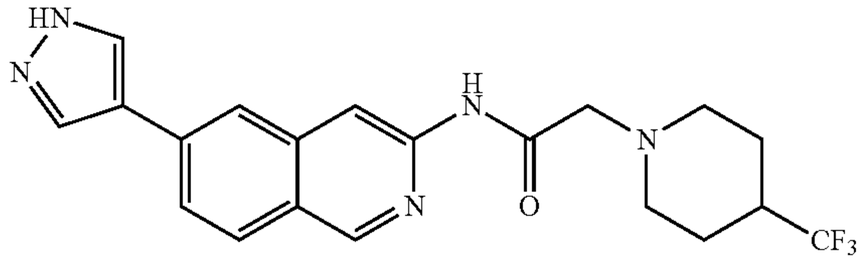
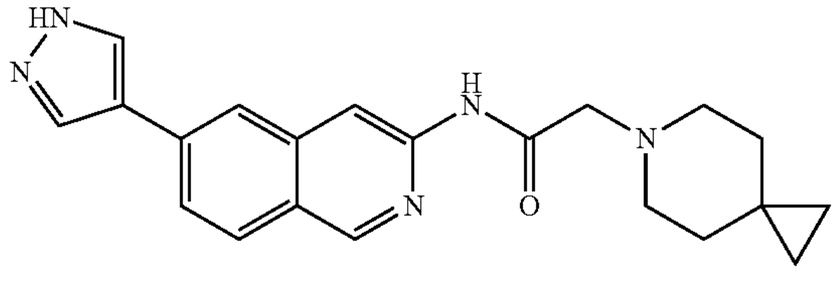
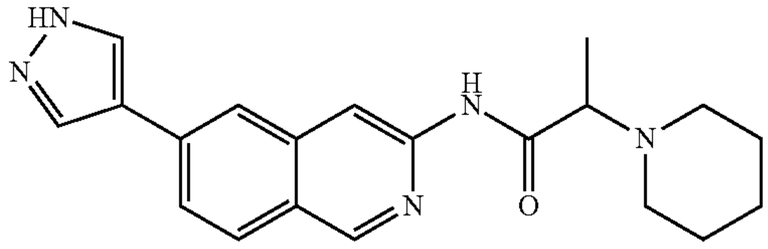
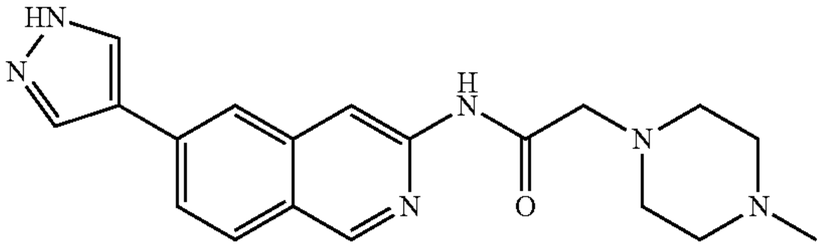
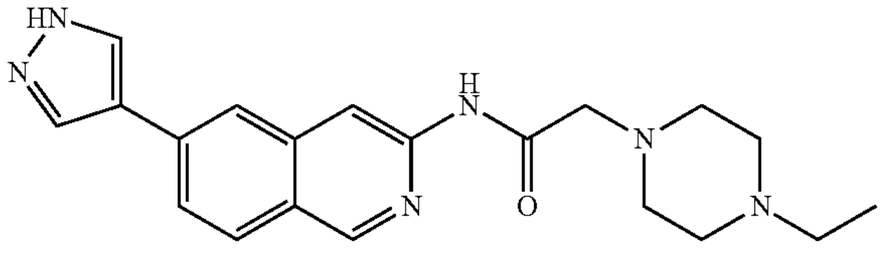
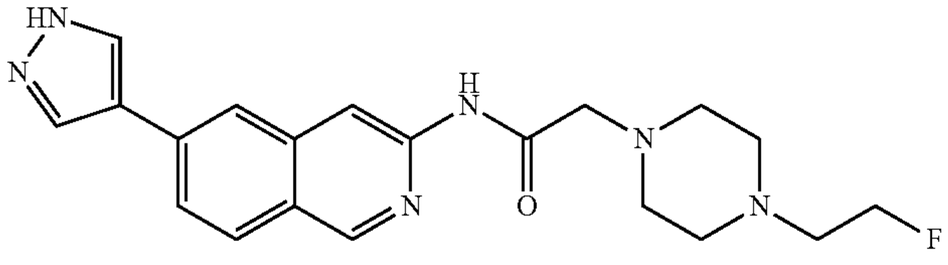
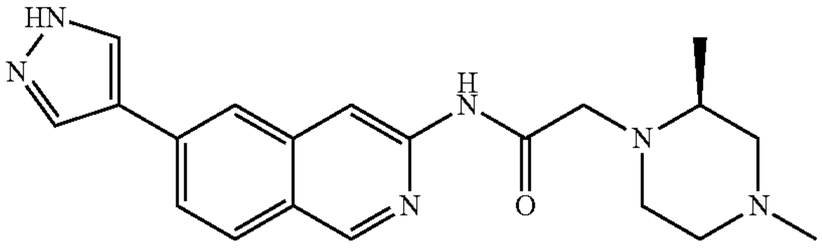
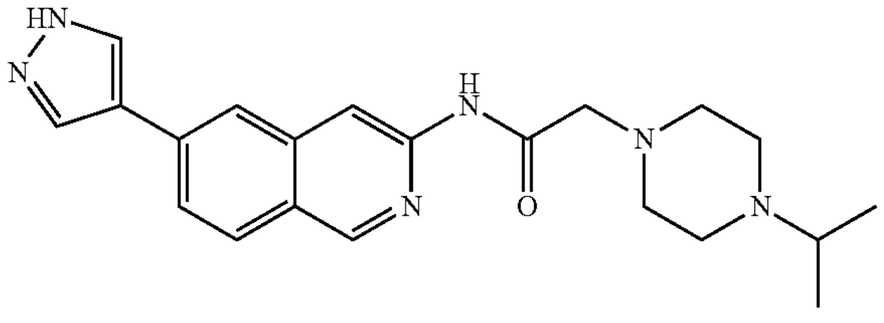
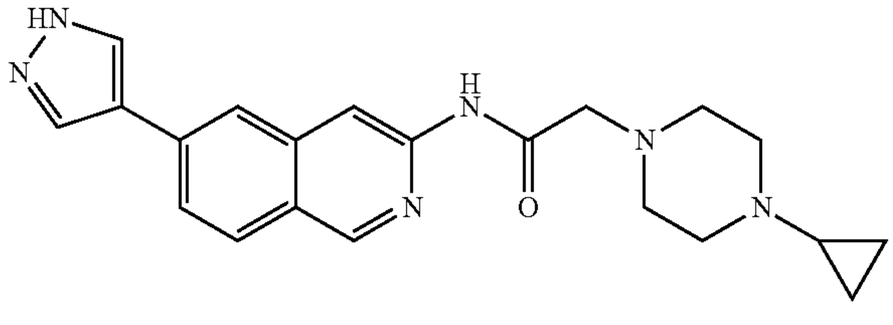
	674
	675
	676
	677
	678
	679
	680
	681
	682

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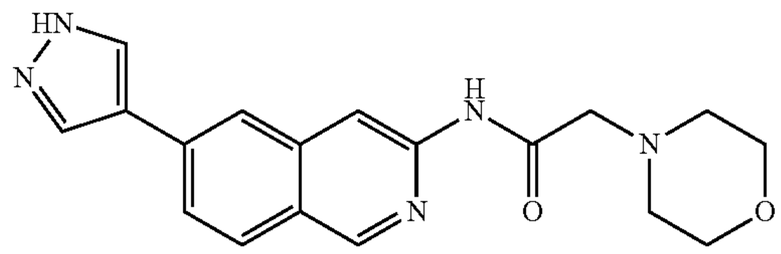
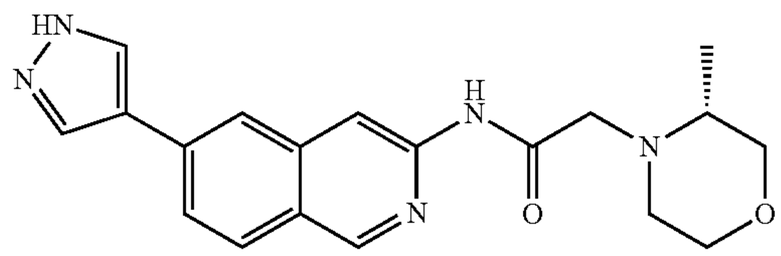
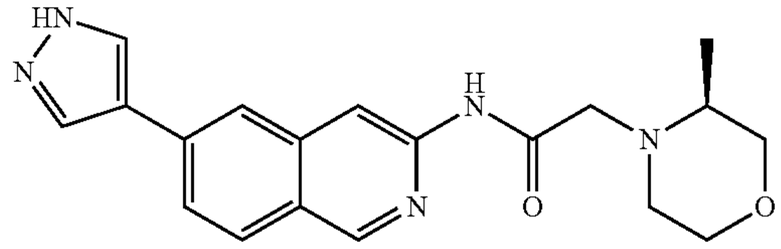
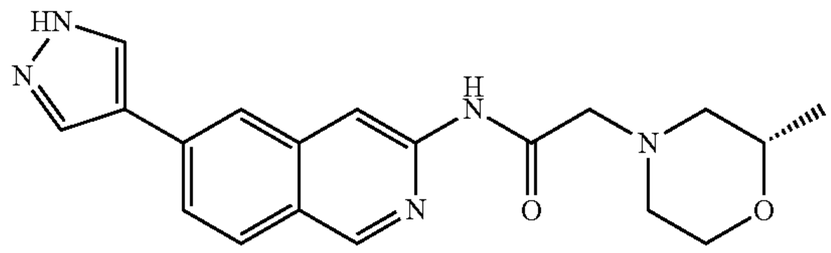
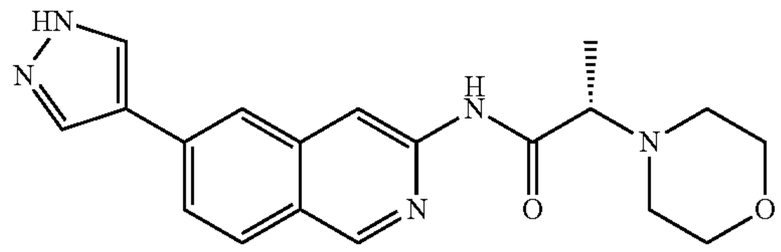
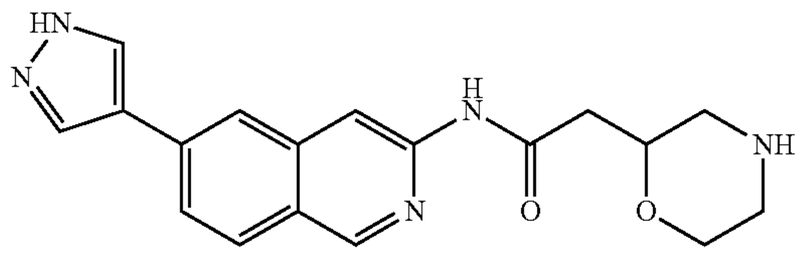
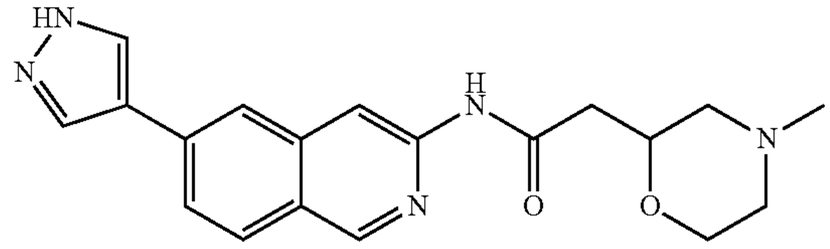
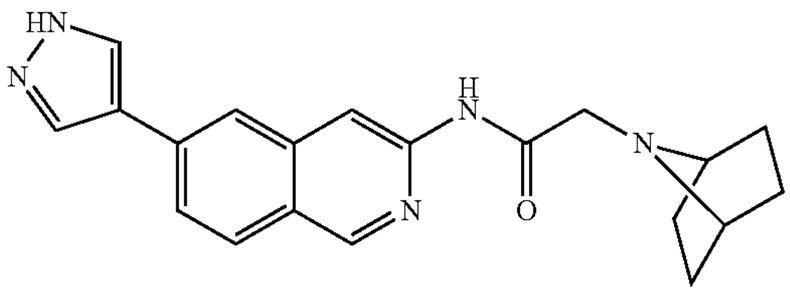
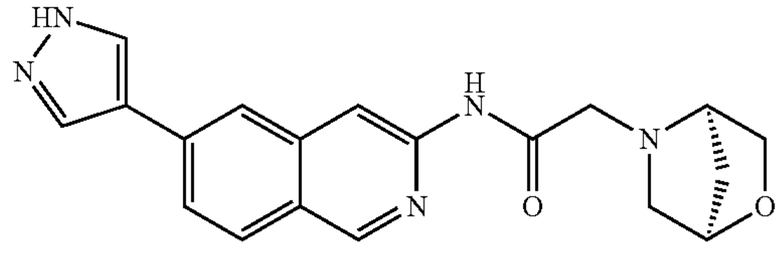
	683
	684
	685
	686
	687
	688
	689
	690
	691

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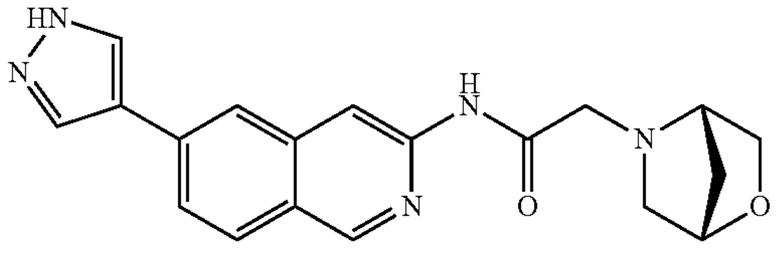
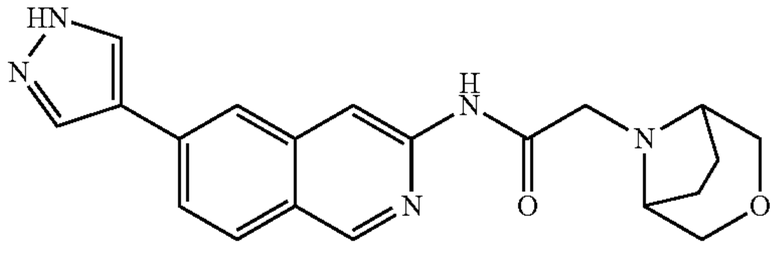
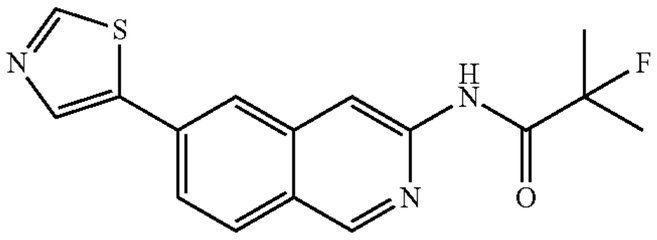
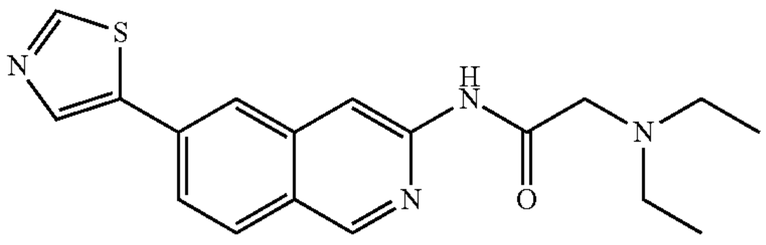
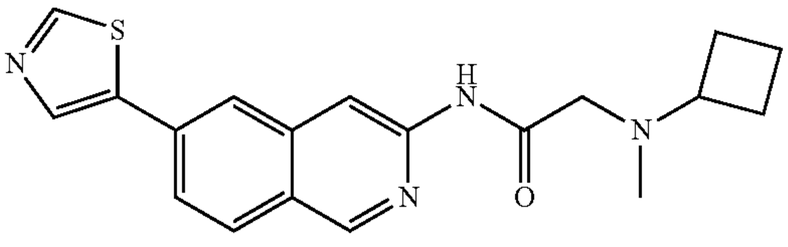
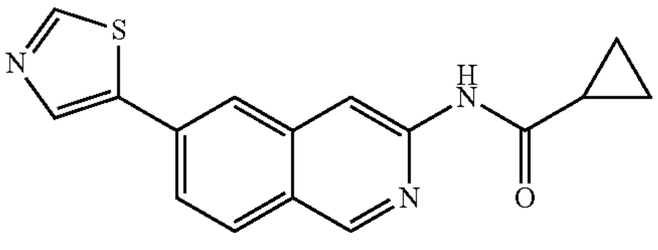
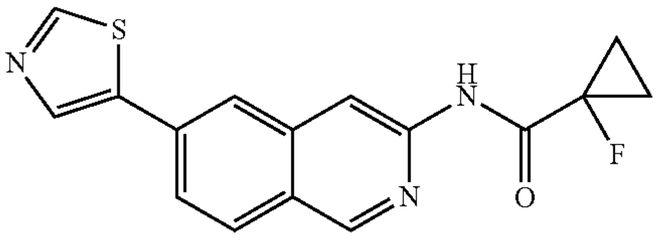
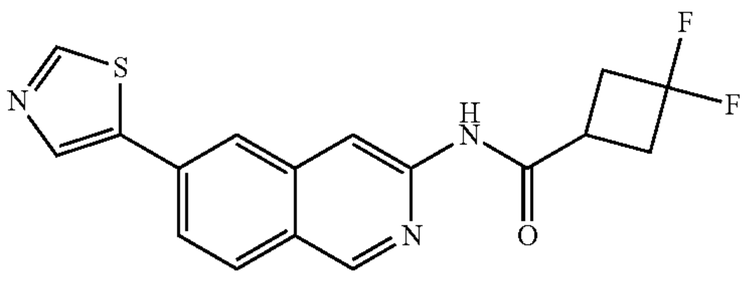
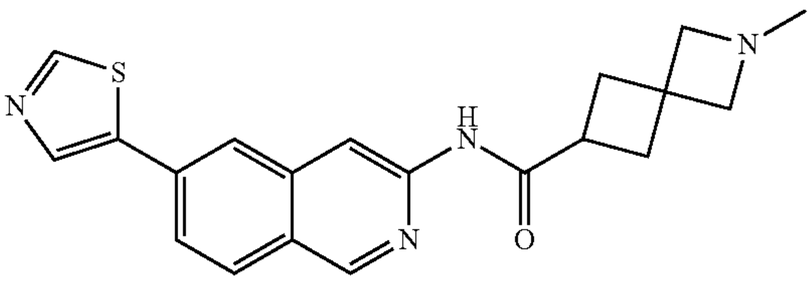
	692
	693
	694
	695
	696
	697
	698
	699
	700

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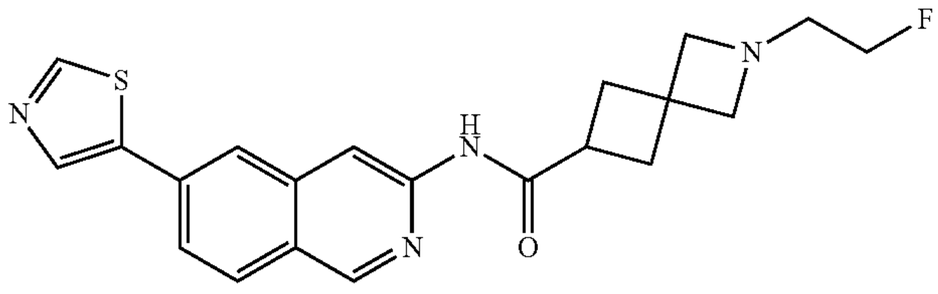
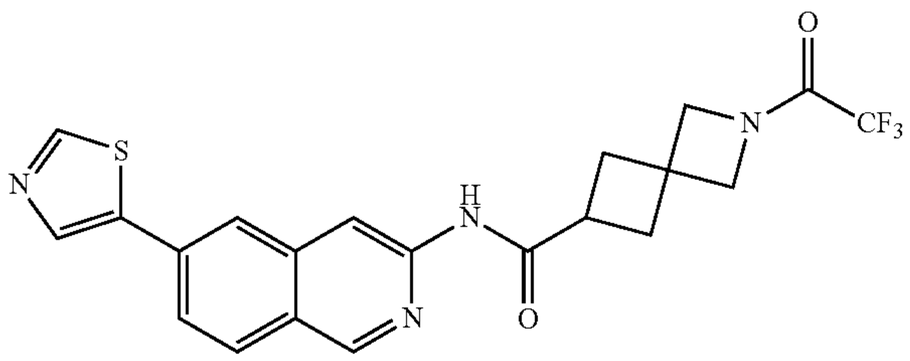
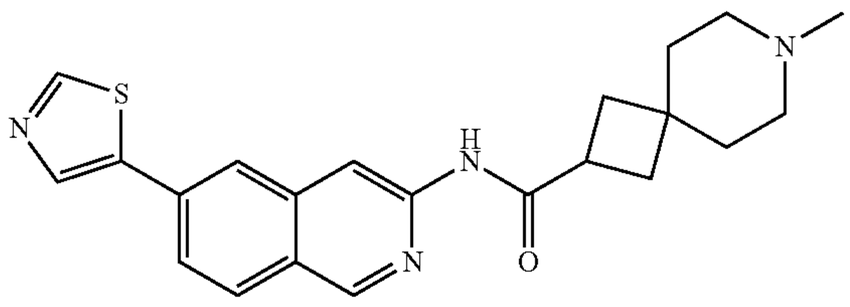
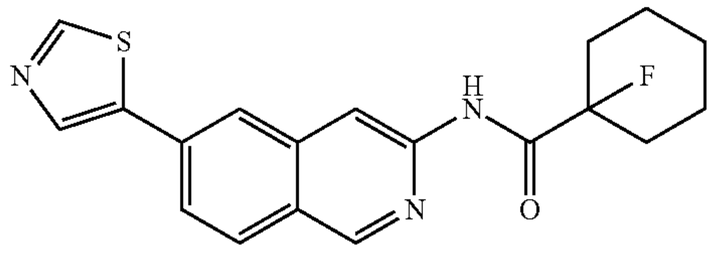
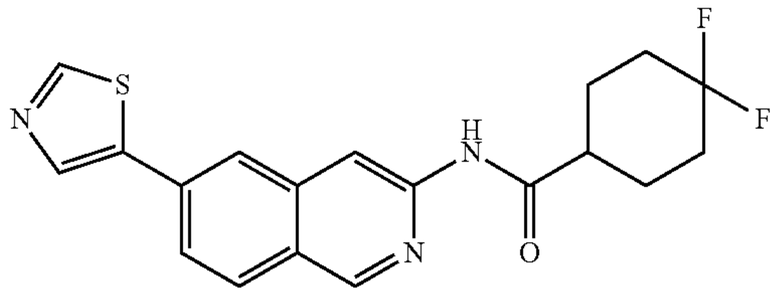
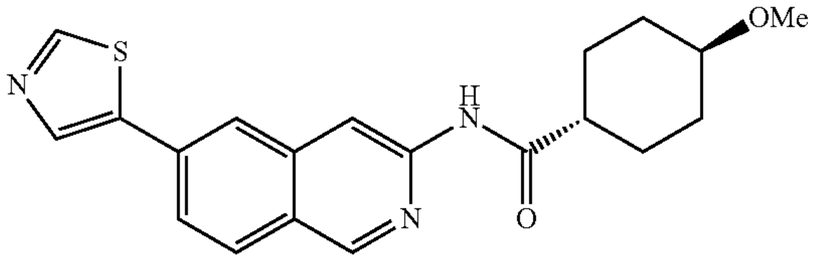
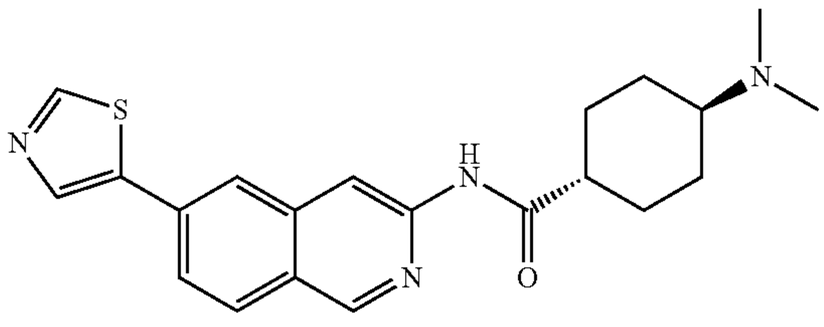
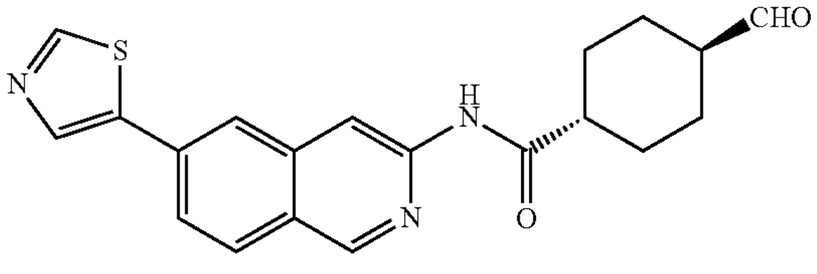
	701
	702
	703
	704
	705
	706
	707
	708

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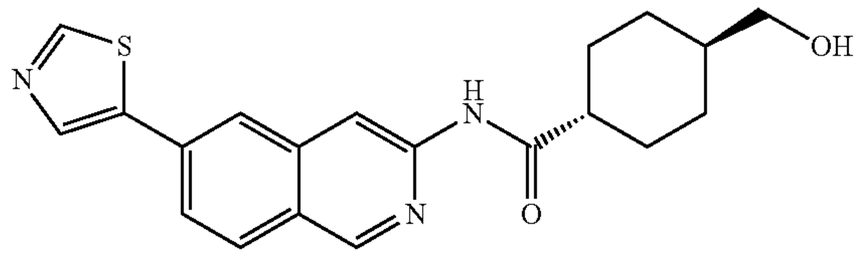

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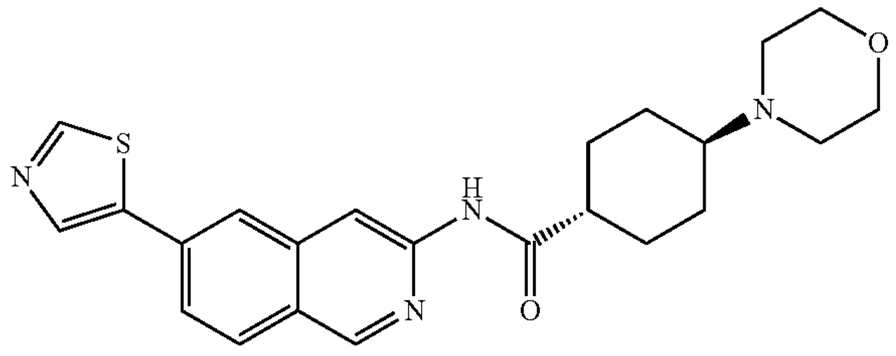

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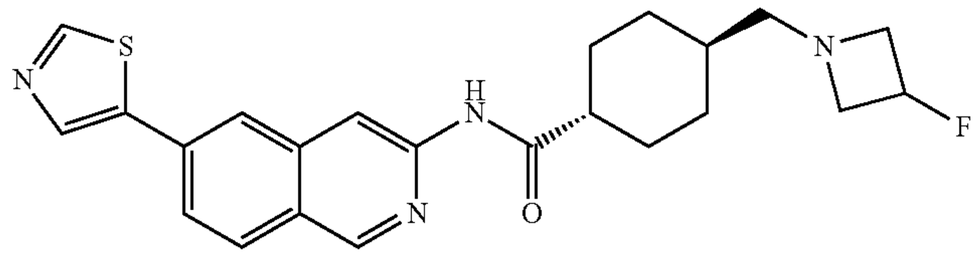

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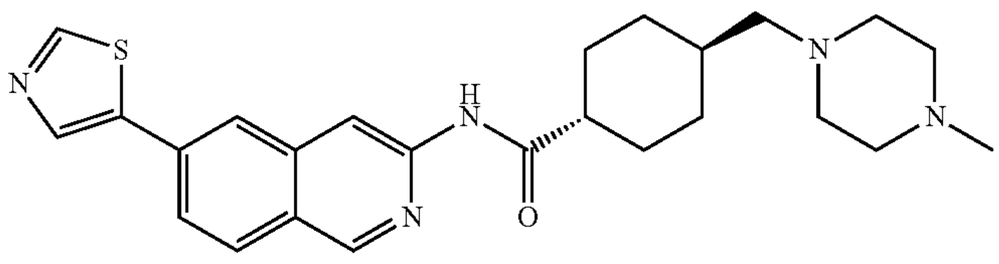

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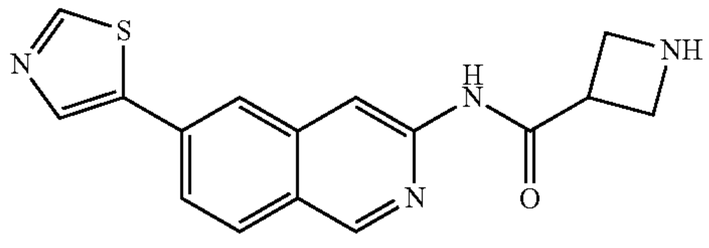

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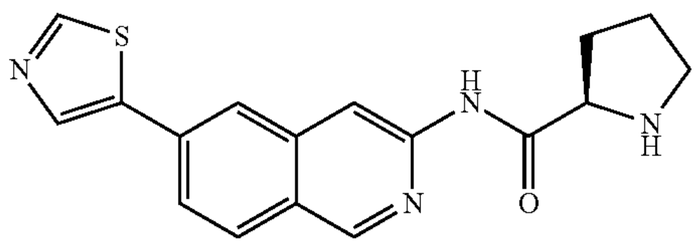

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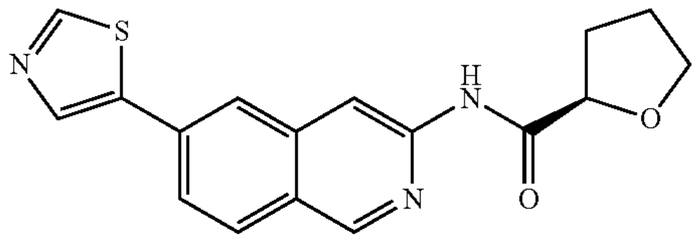

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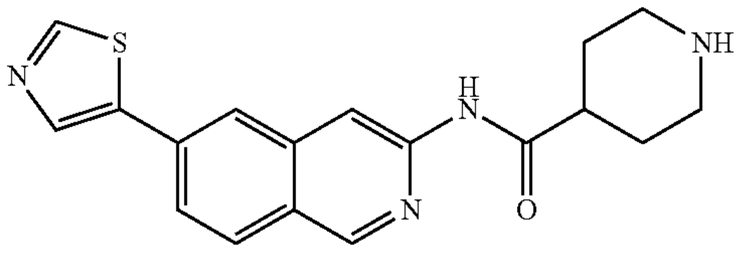

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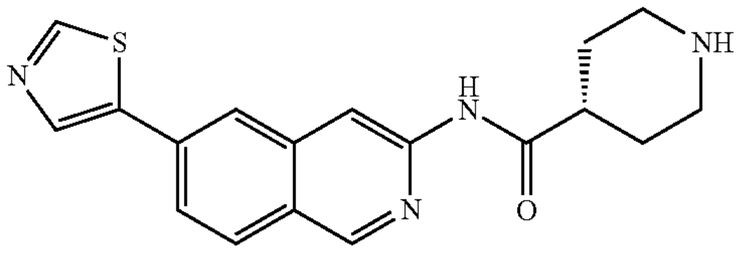

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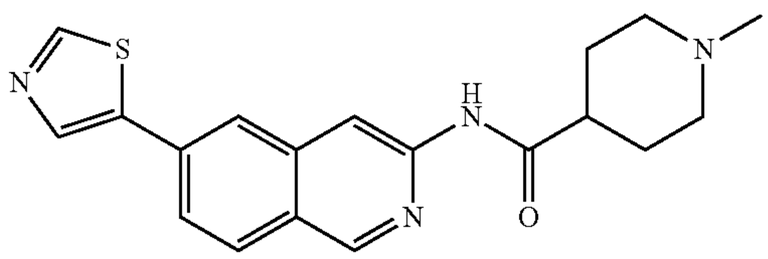
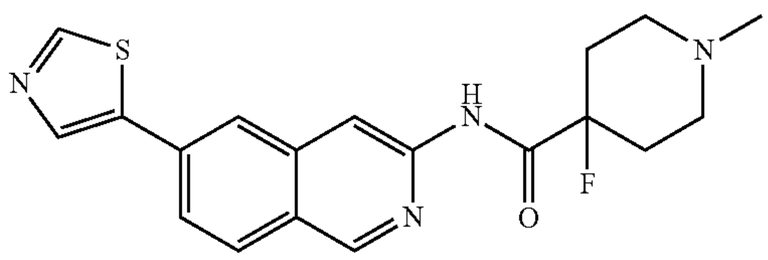
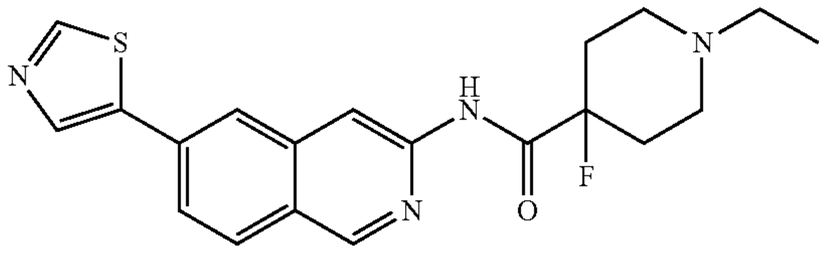
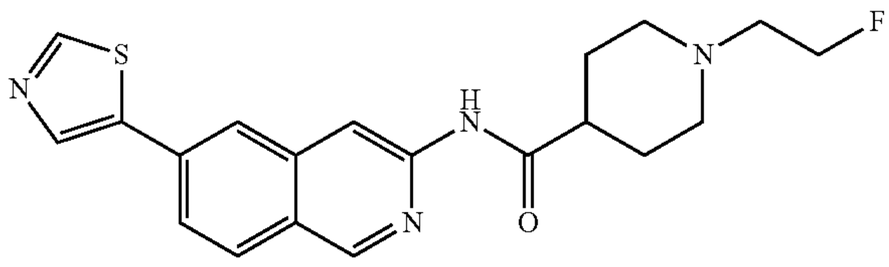
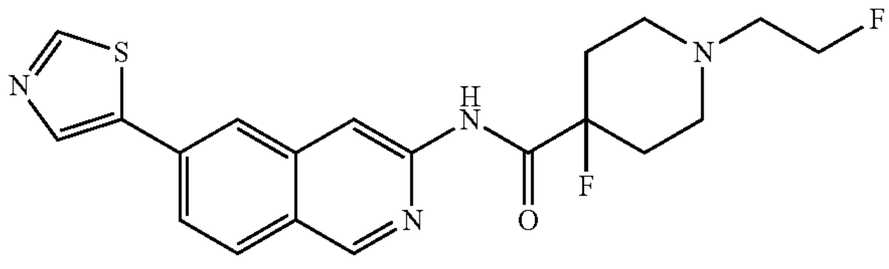
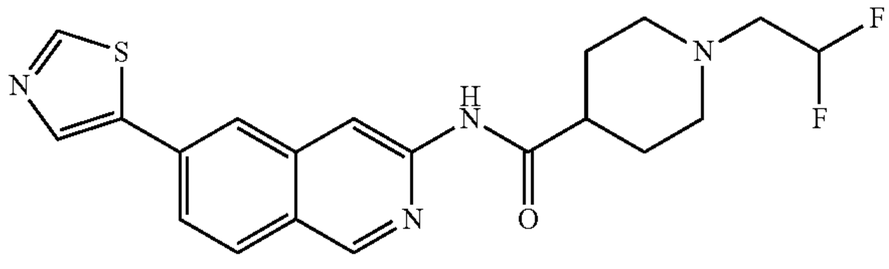
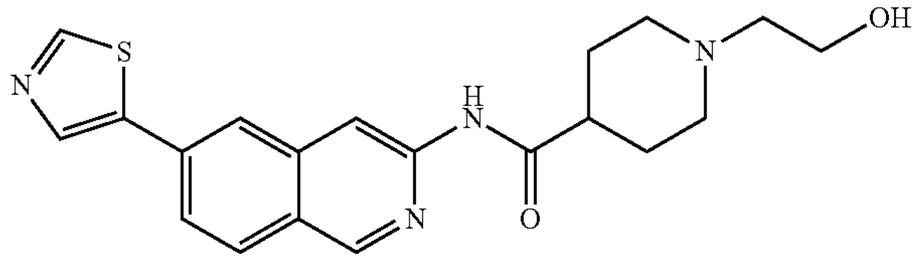
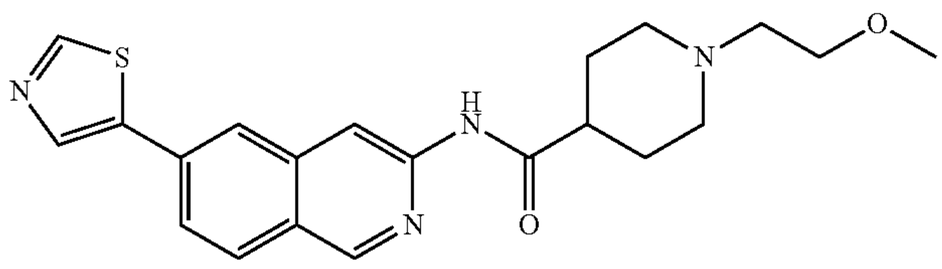
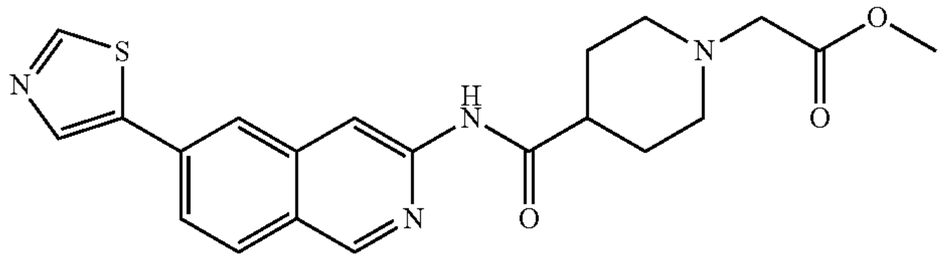
	718
	719
	720
	721
	722
	723
	724
	725
	726

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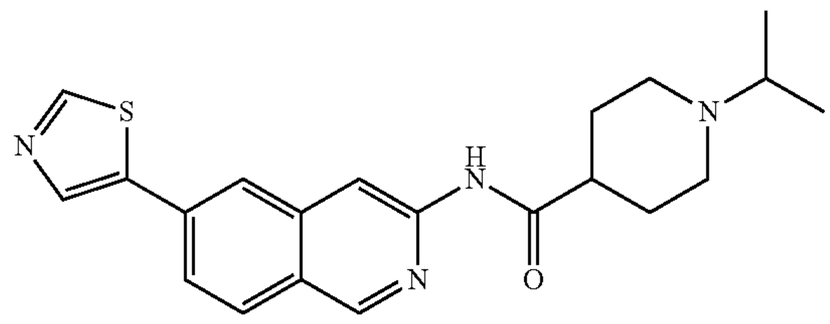

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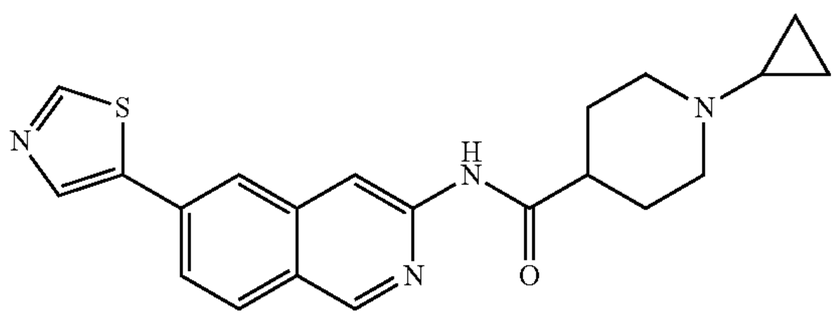

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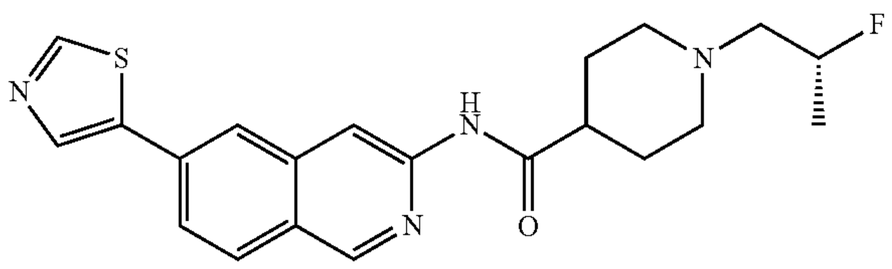

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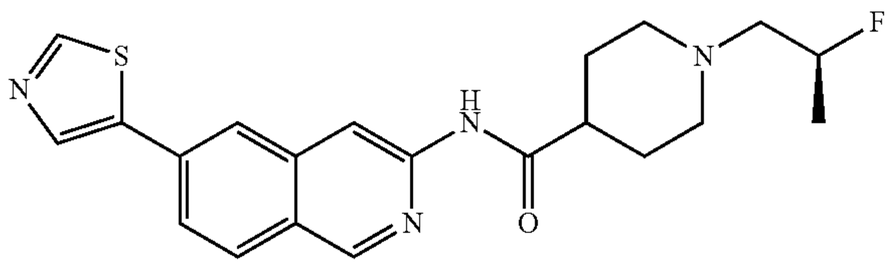

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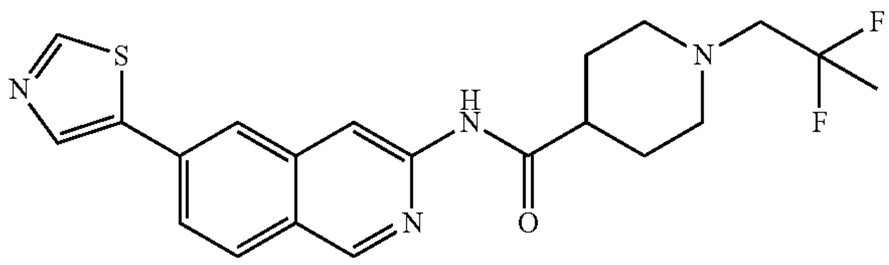

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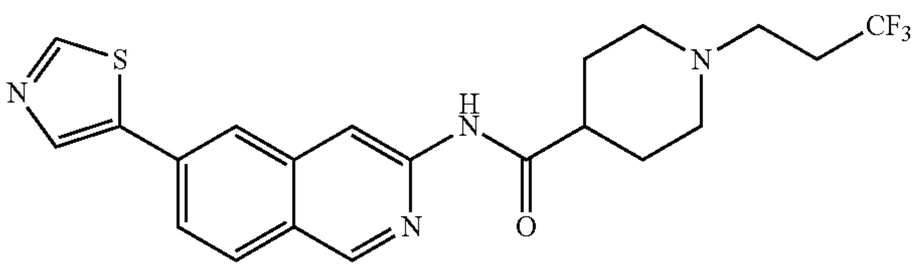

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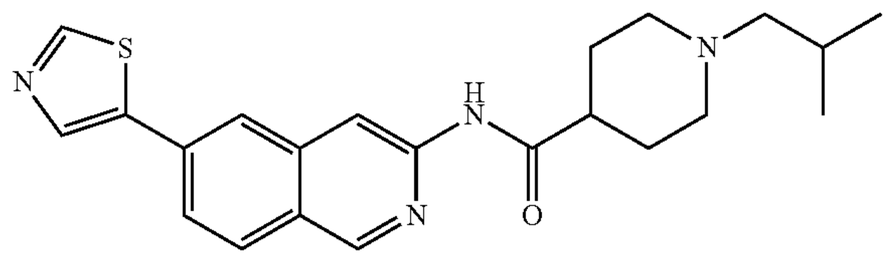

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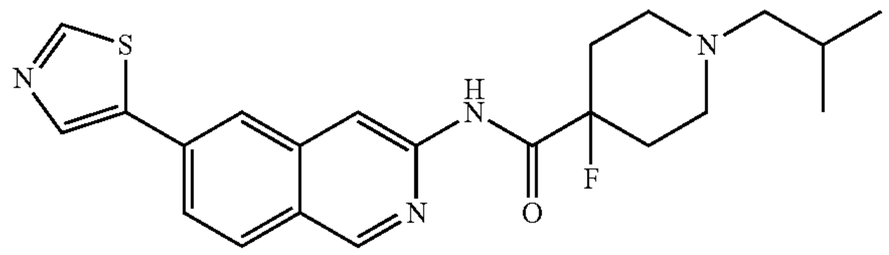

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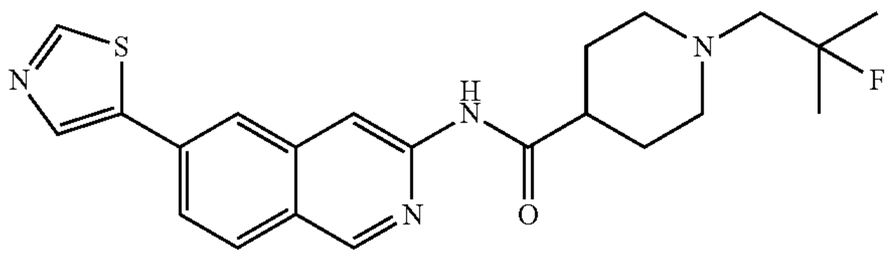

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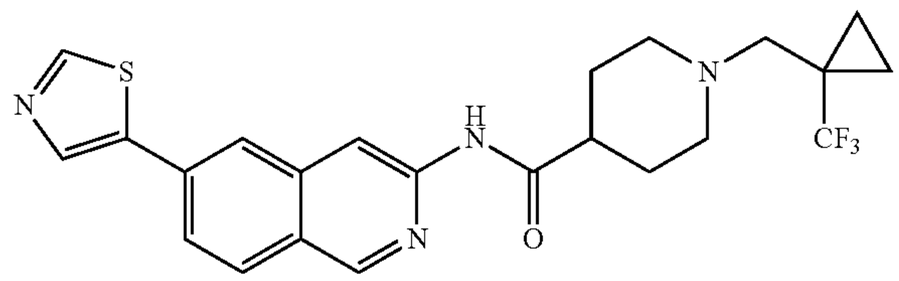

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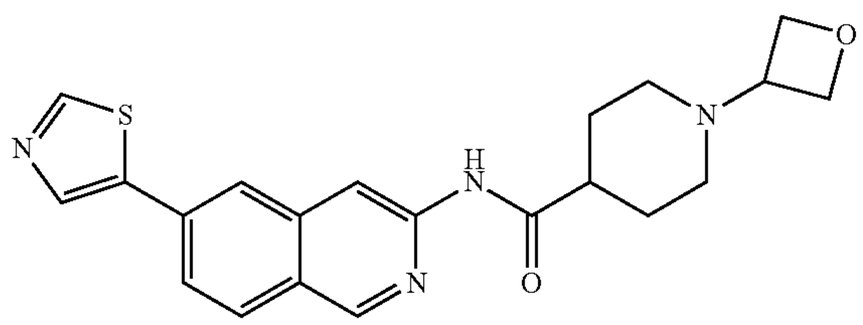

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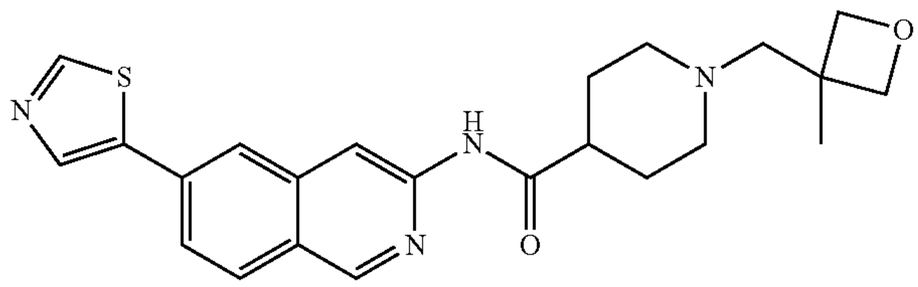

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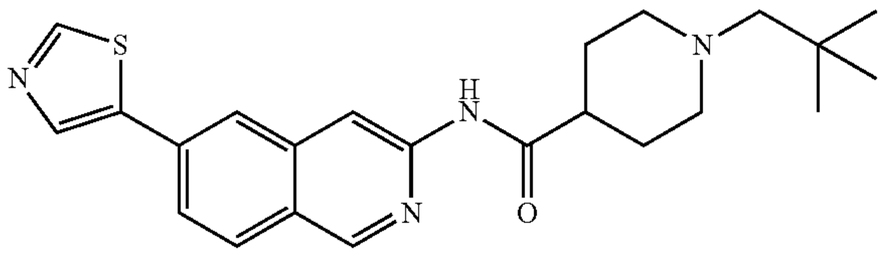

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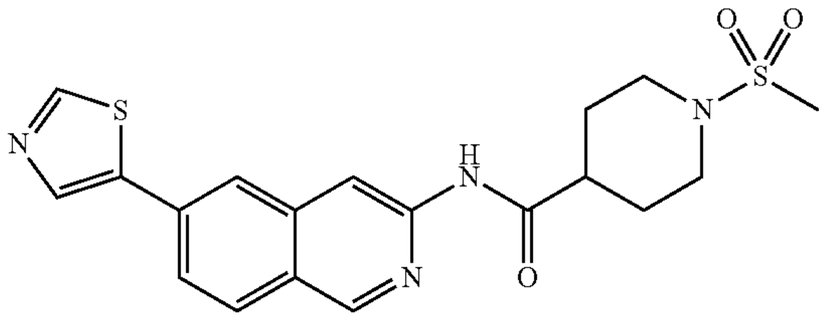

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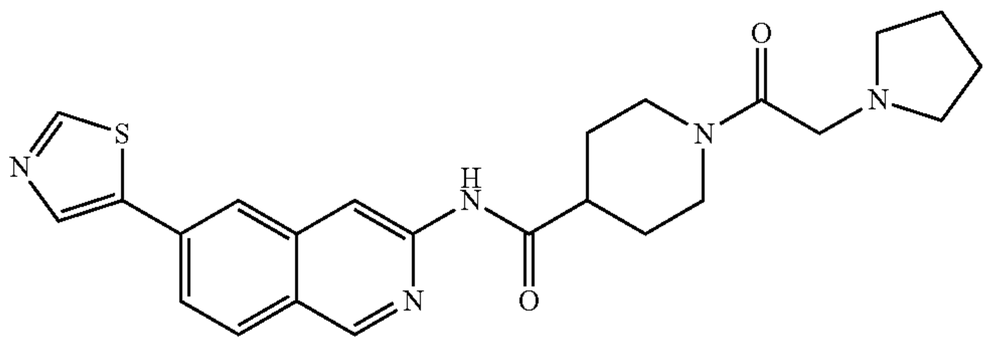

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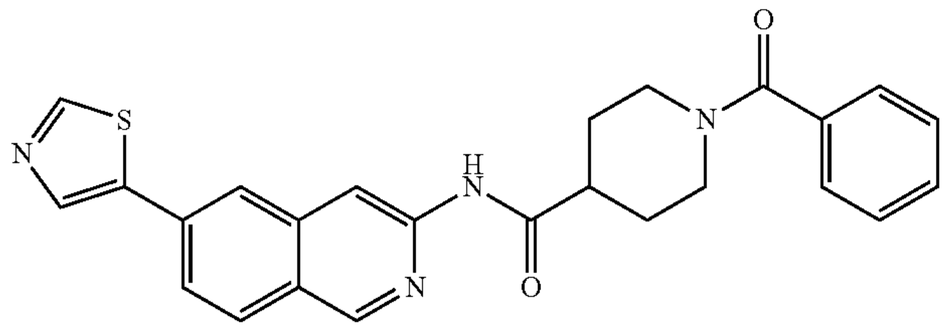

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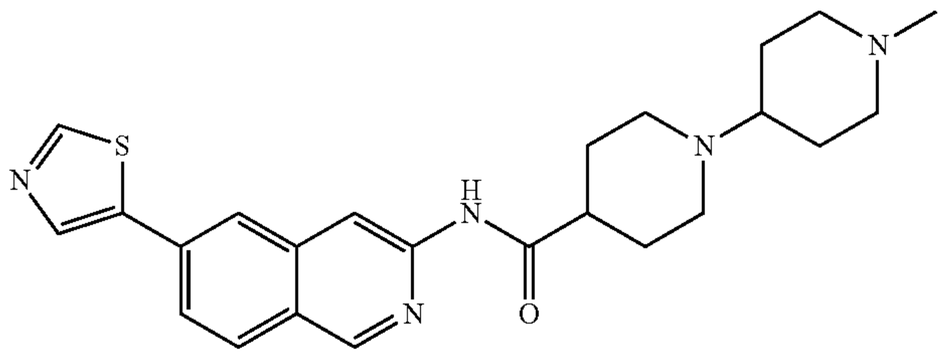

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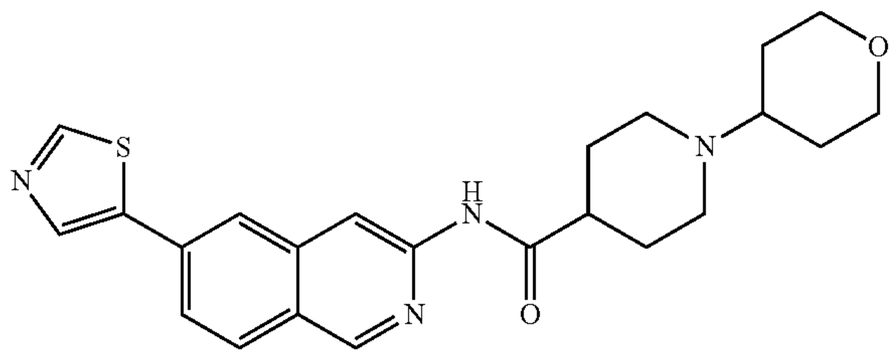

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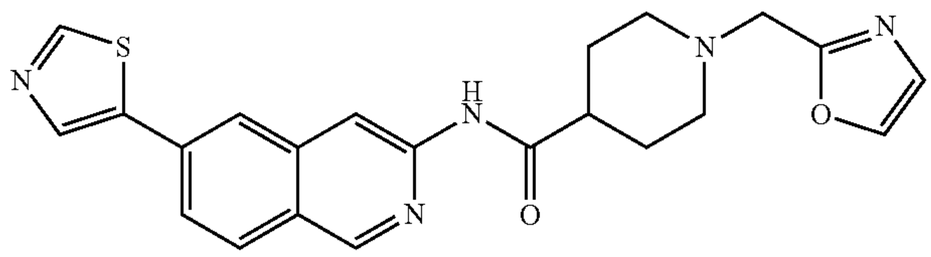

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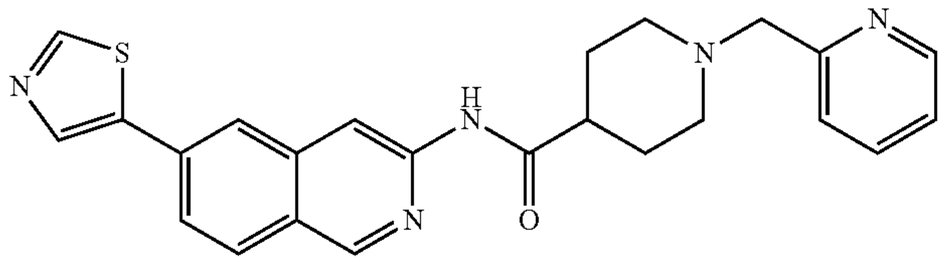

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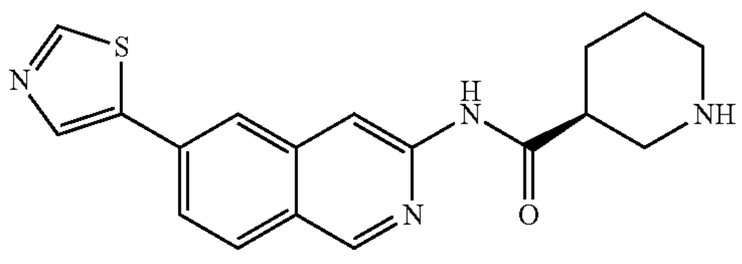

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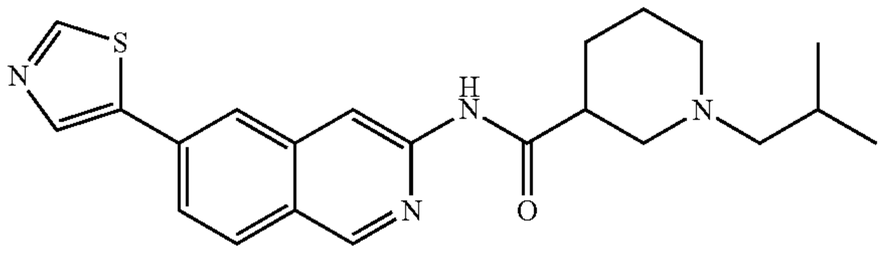

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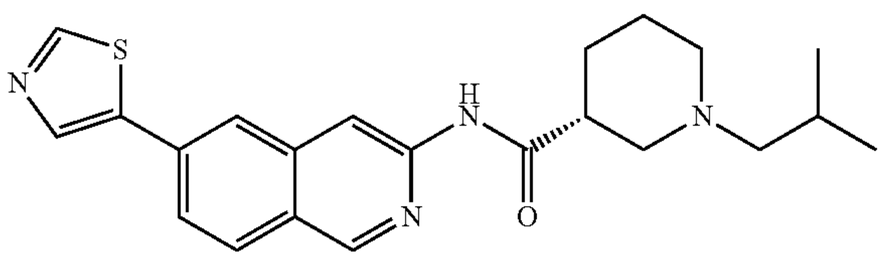

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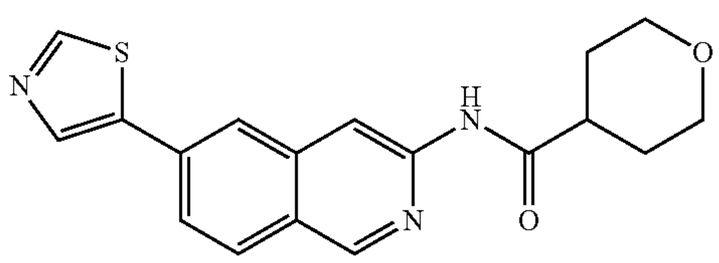

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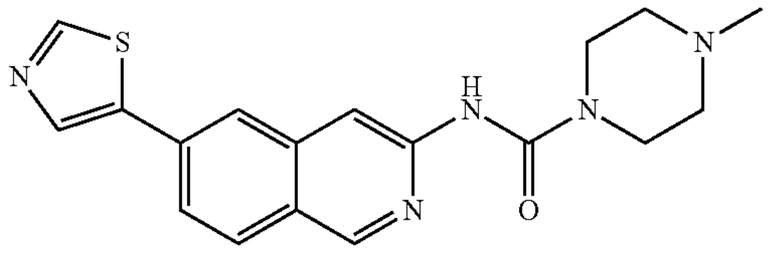

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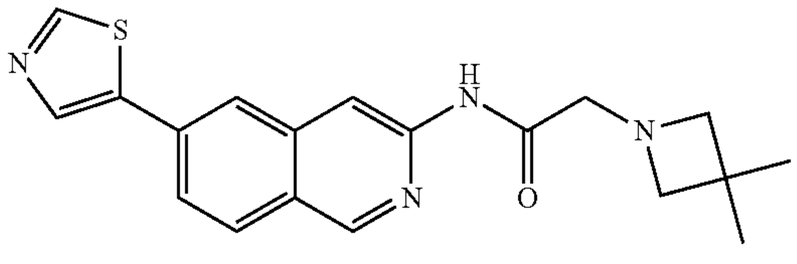

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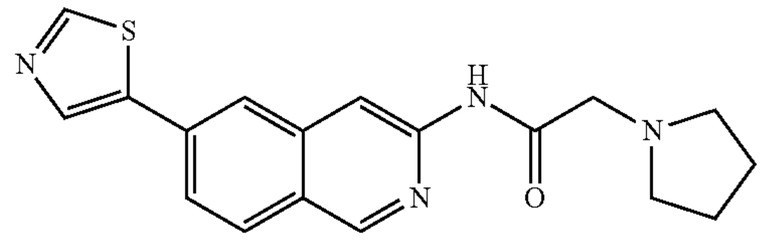

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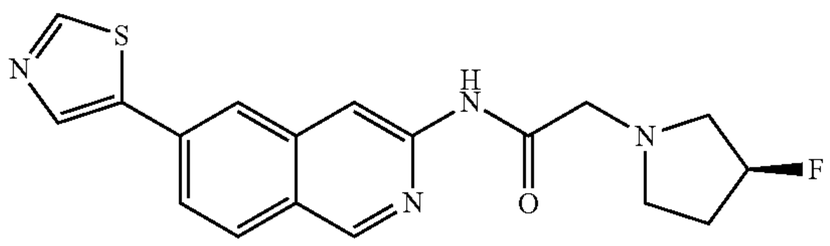

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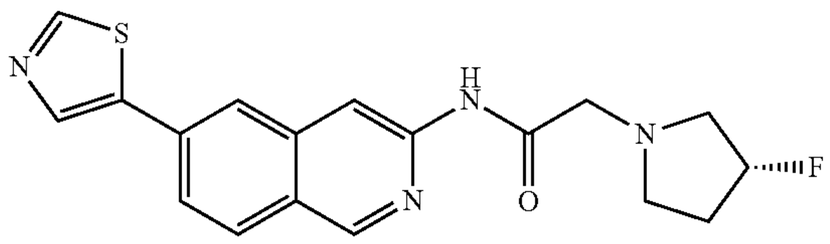

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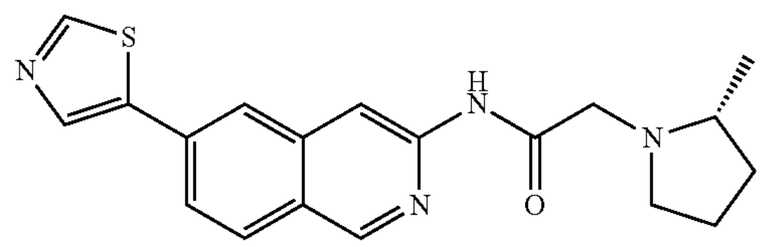

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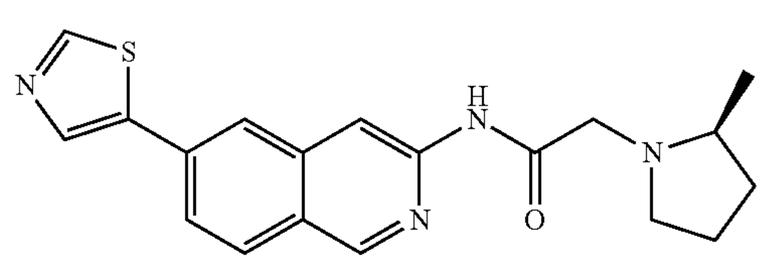

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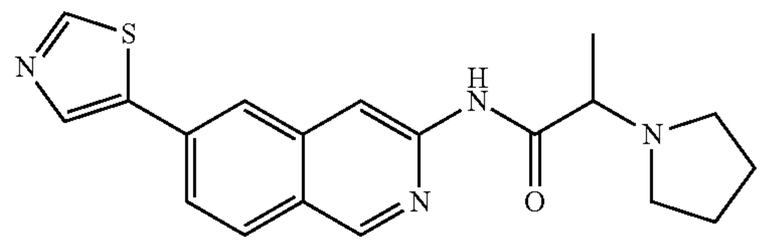

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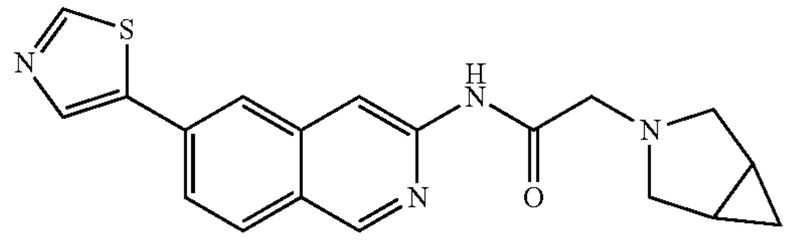

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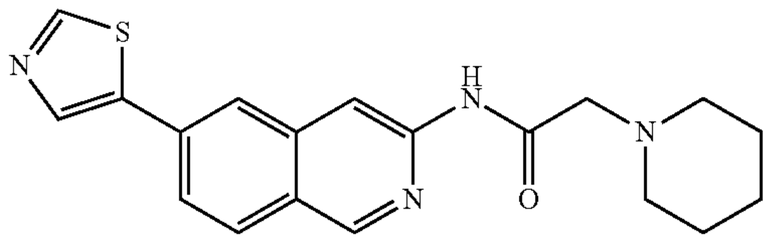

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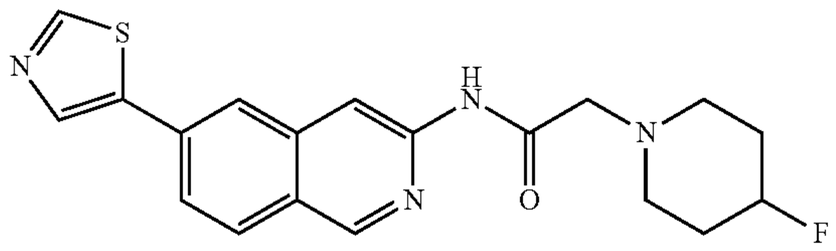

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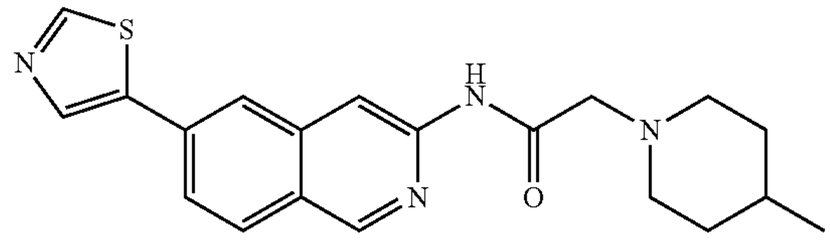

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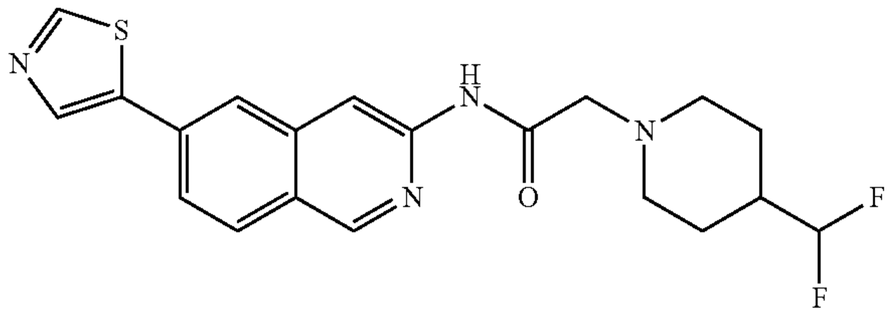

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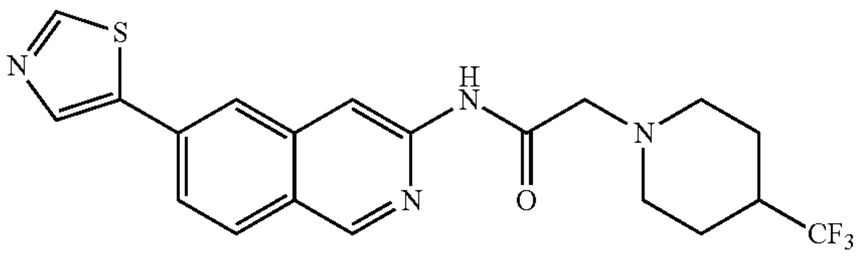

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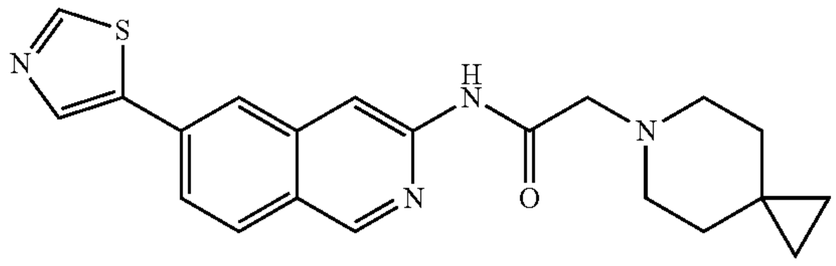

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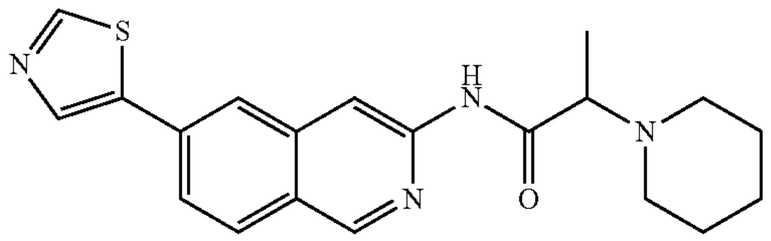

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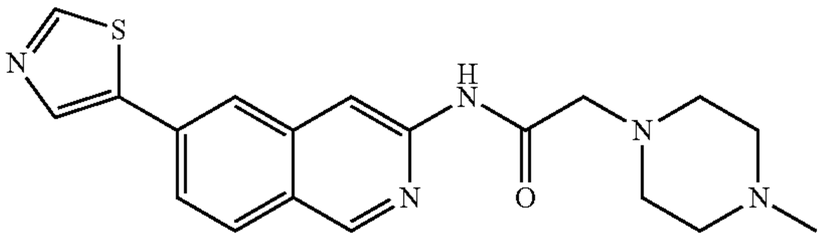

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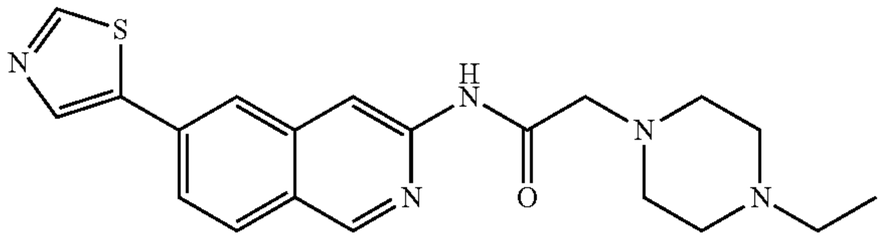

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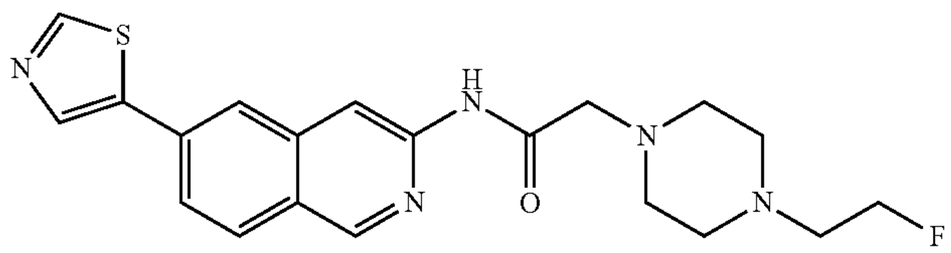
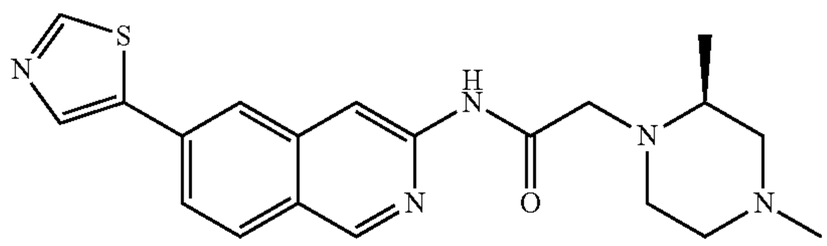
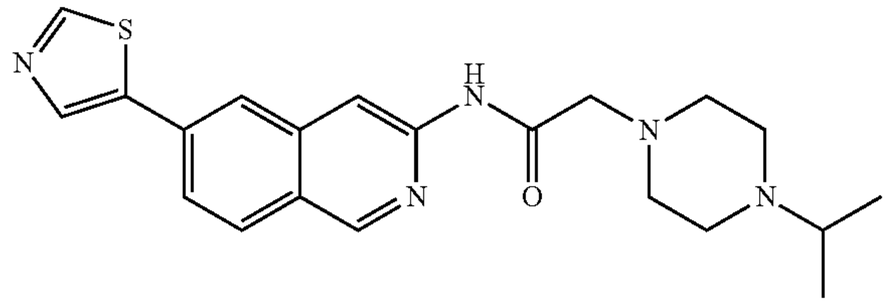
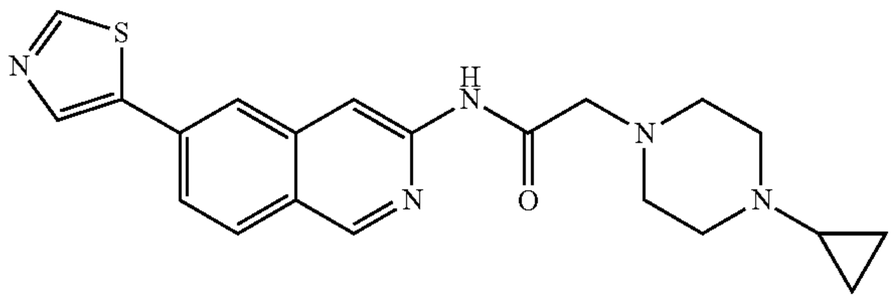
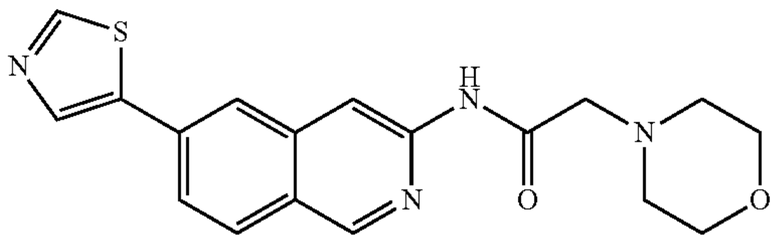
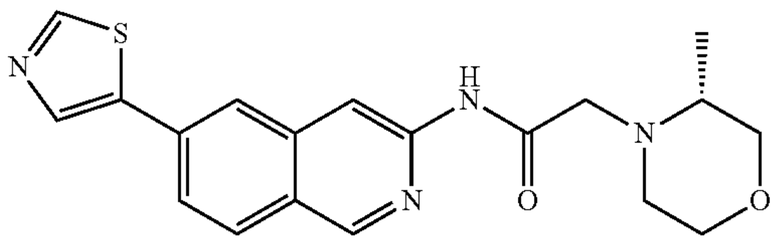
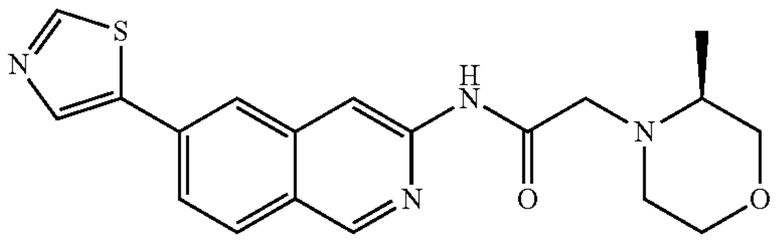
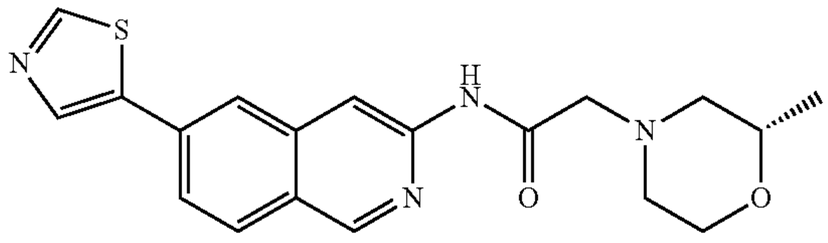
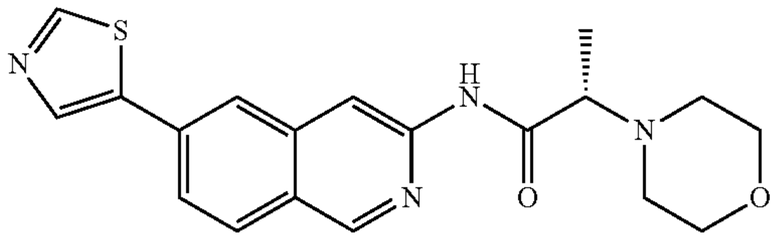
	769
	770
	771
	772
	773
	774
	775
	776
	777

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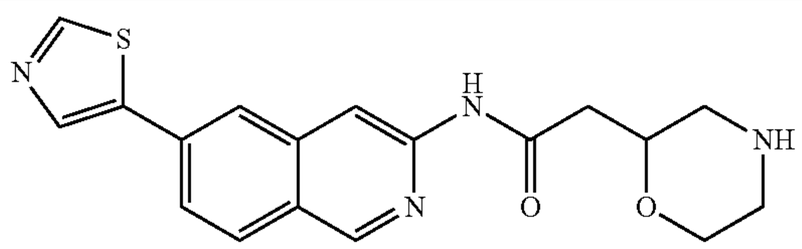
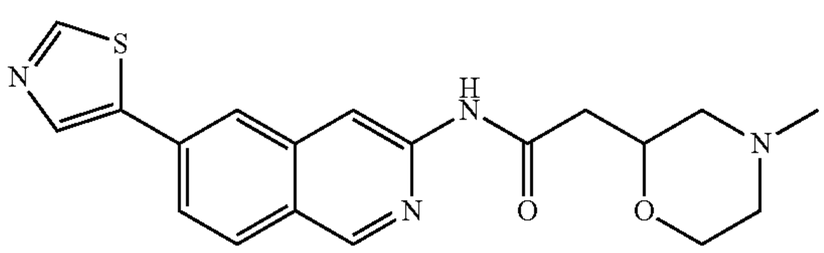
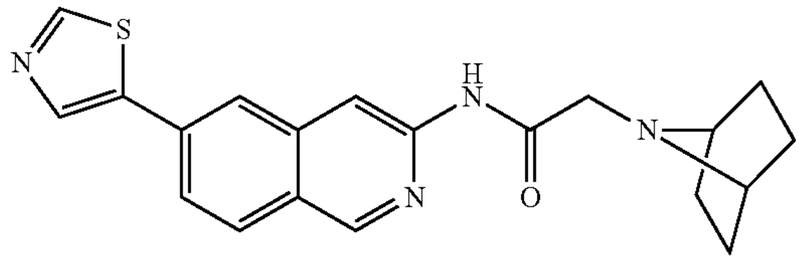
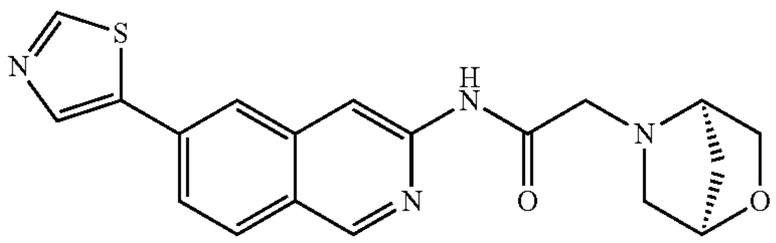
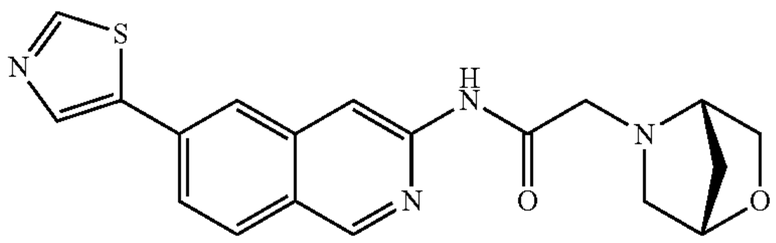
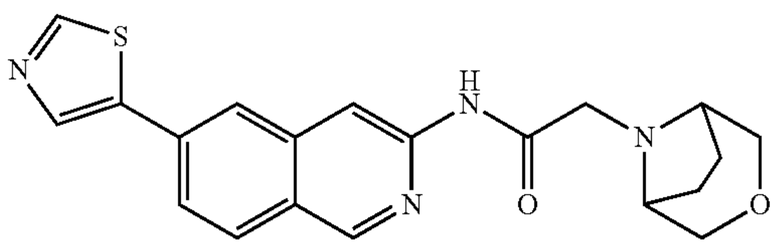
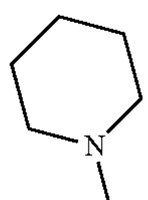
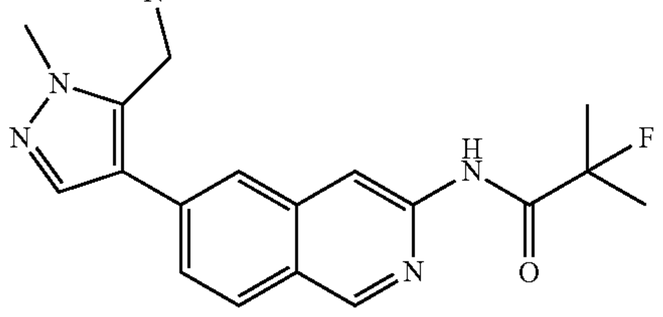
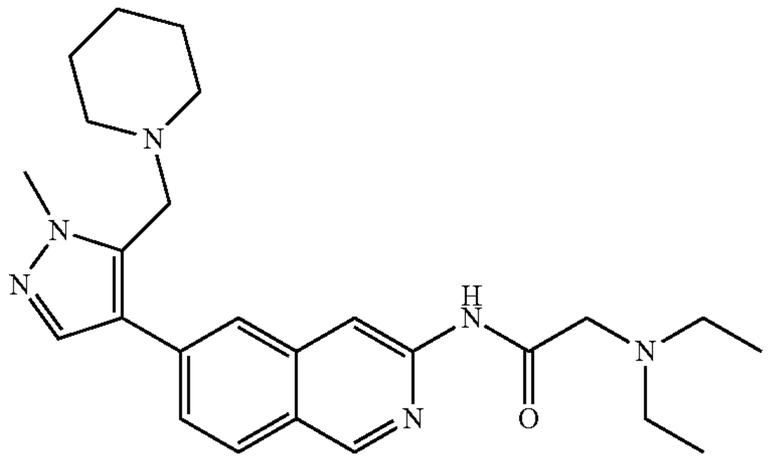
	778
	779
	780
	781
	782
	783
	784
	785
	

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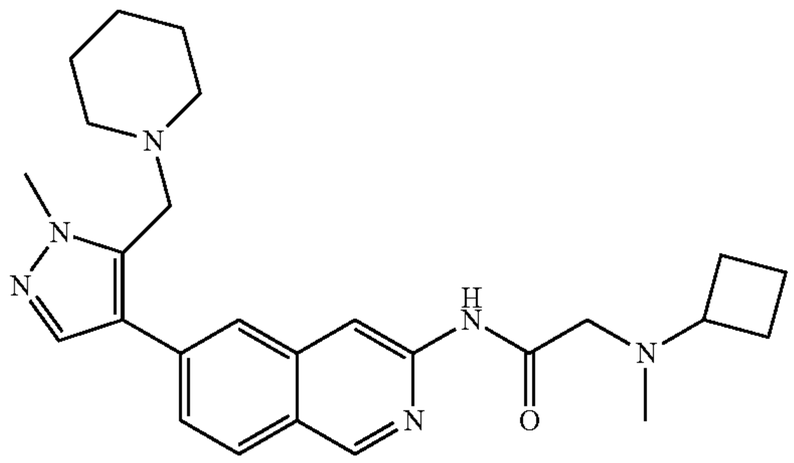
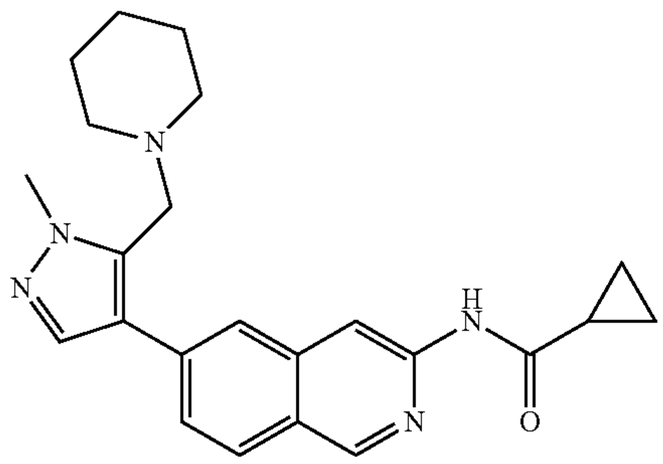
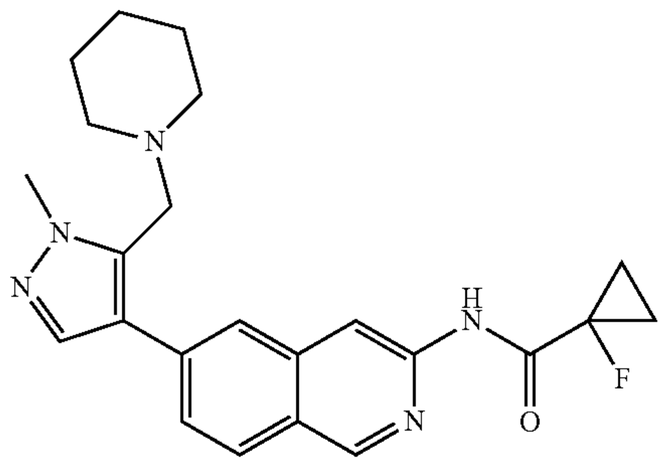
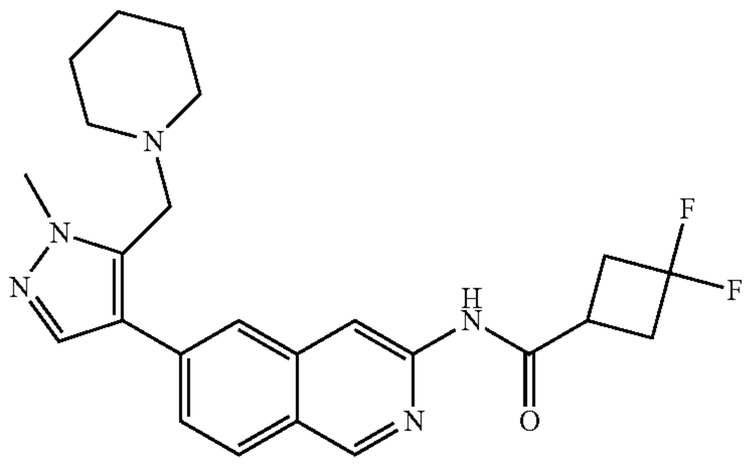
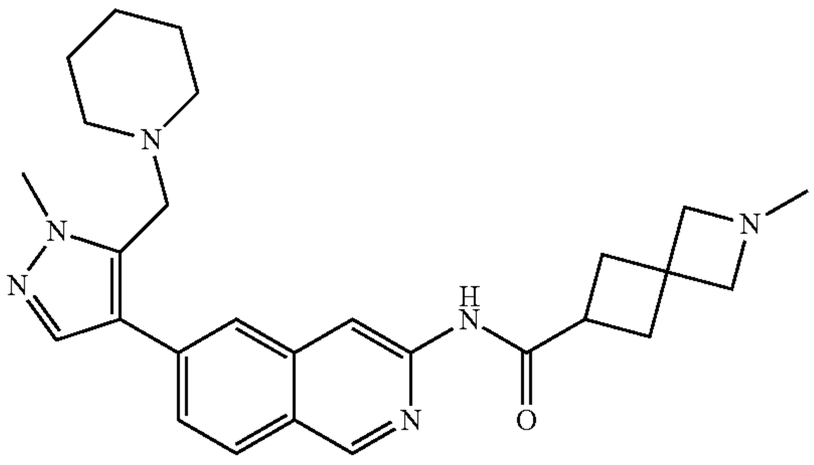
786	
787	
788	
789	
790	

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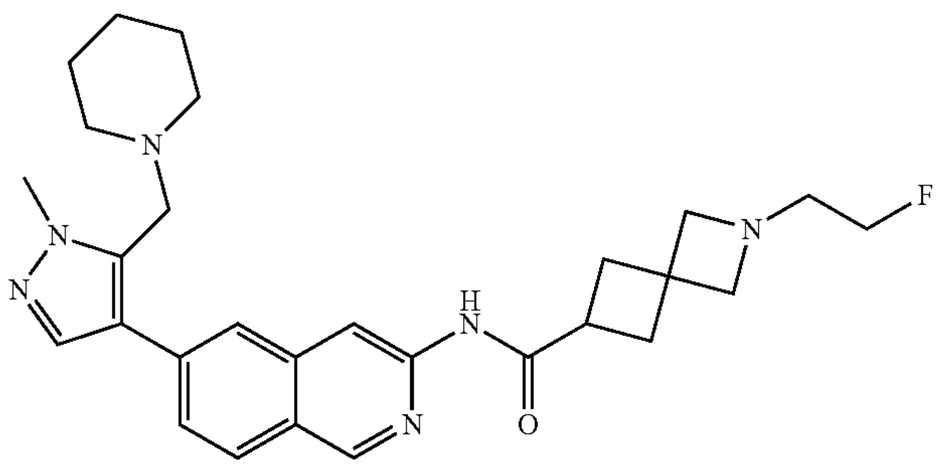	
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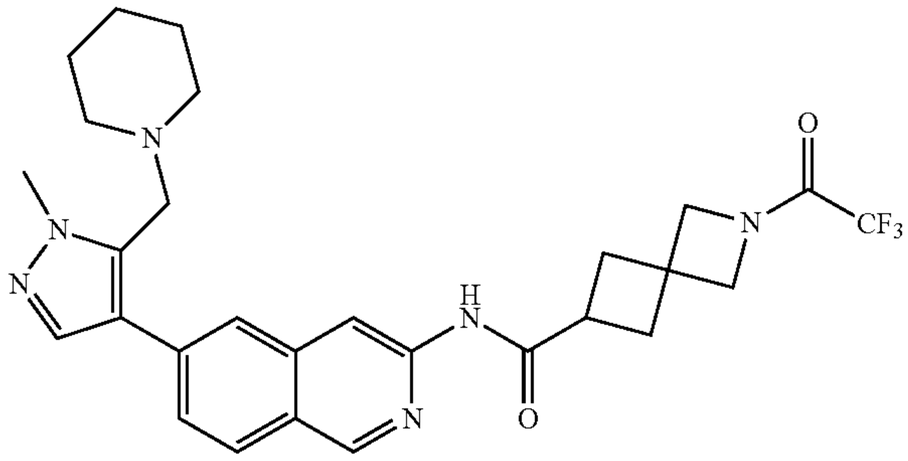	
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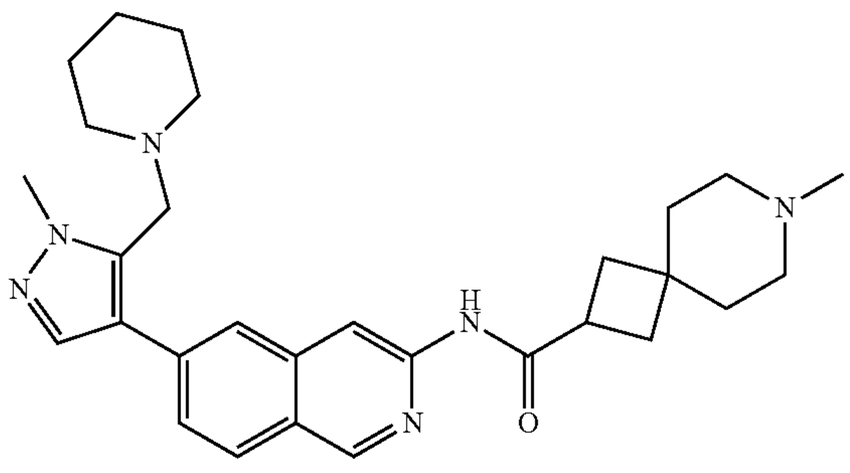	
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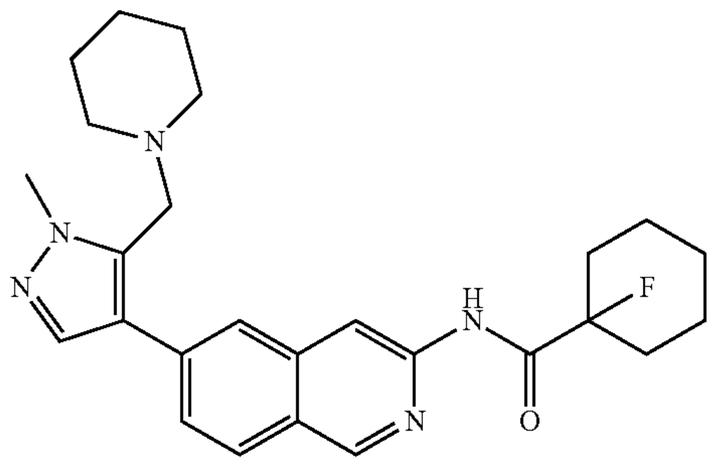	
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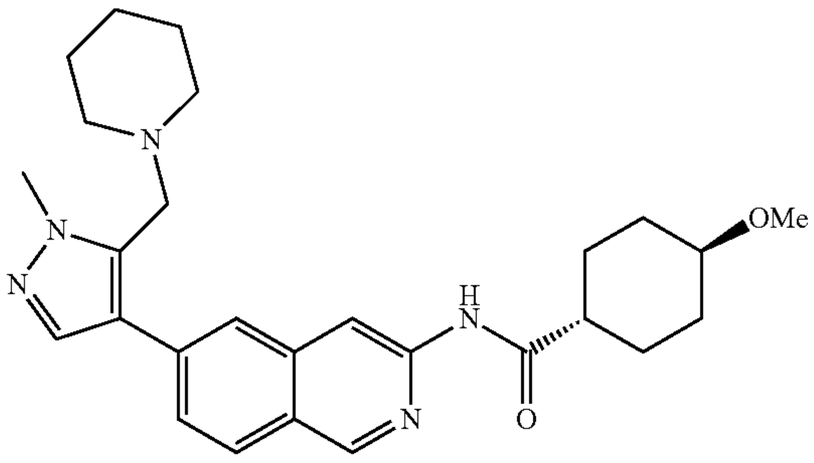	

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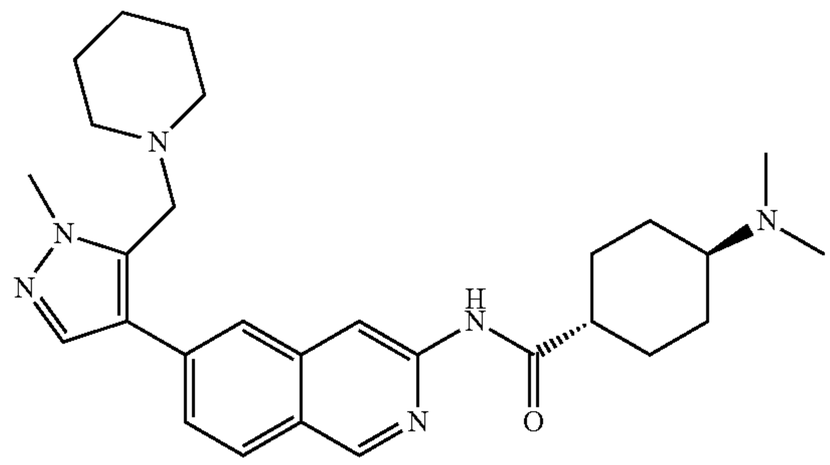

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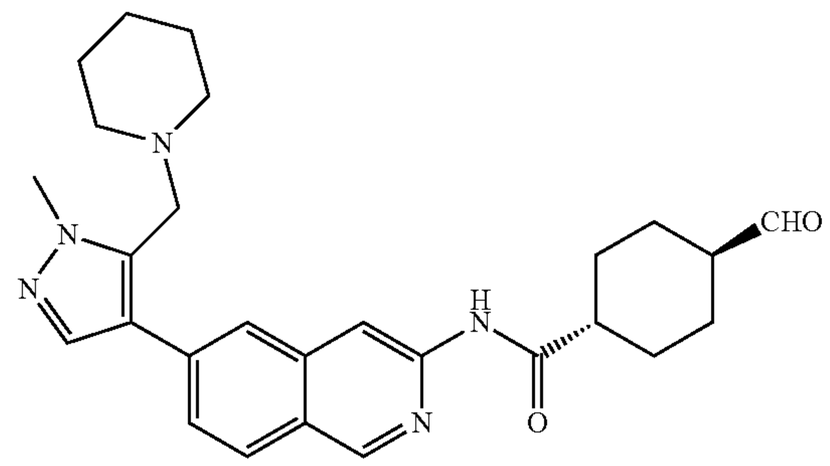

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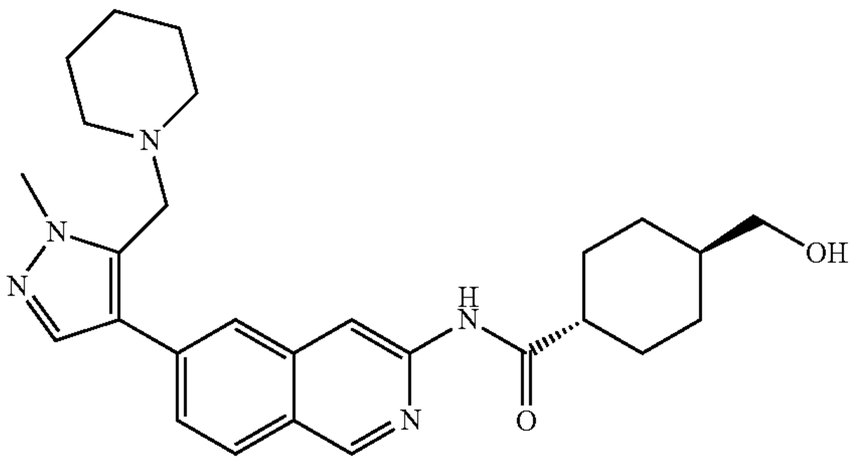

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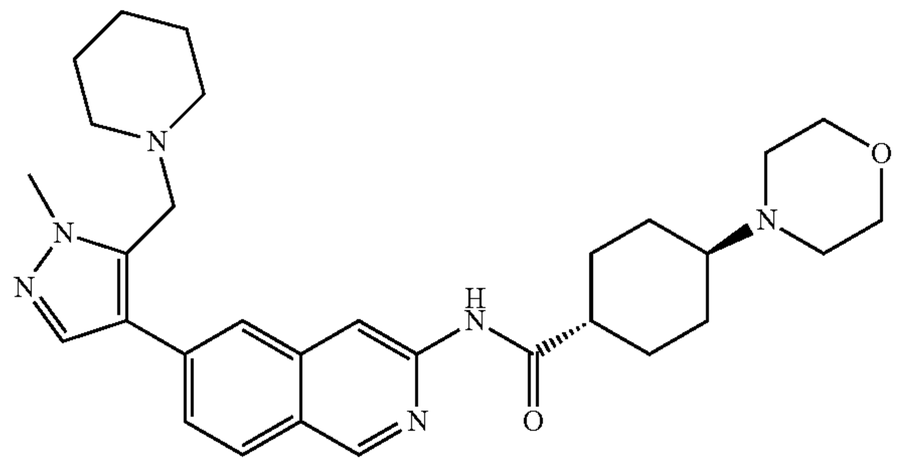

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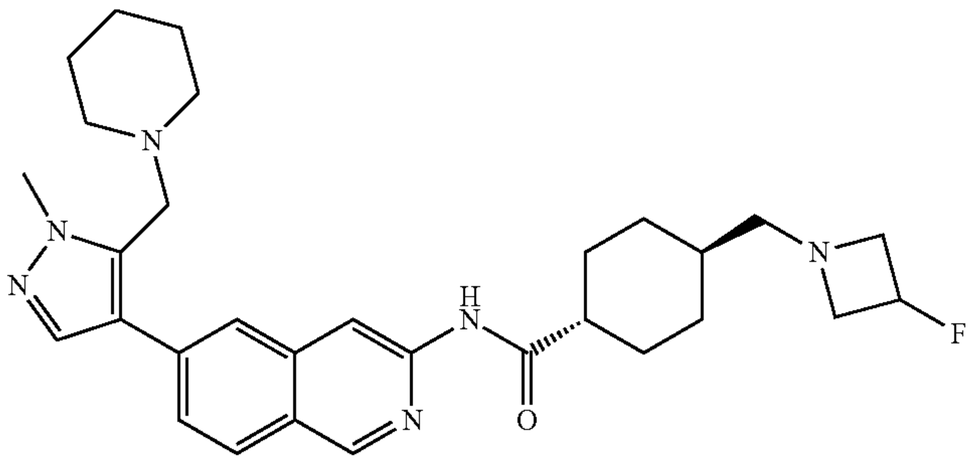

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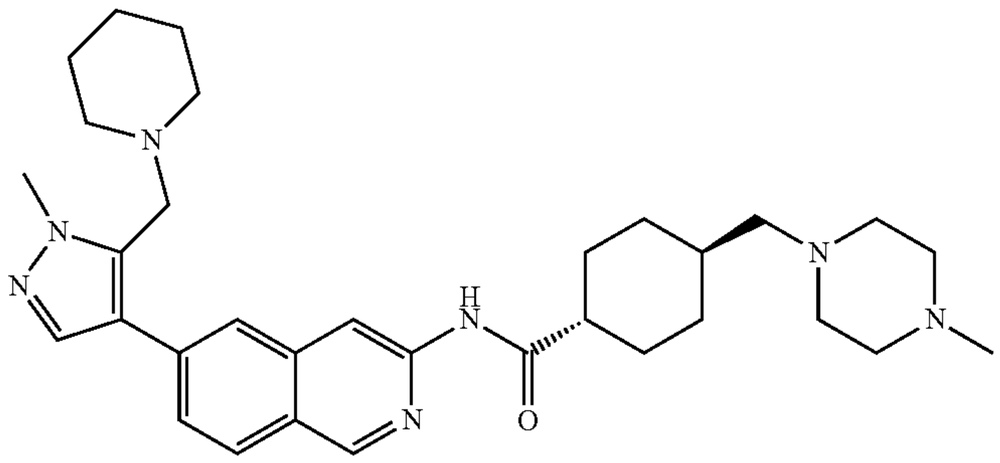
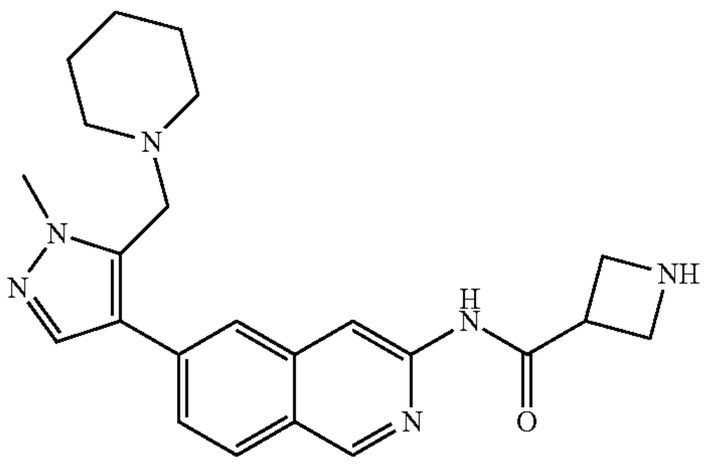
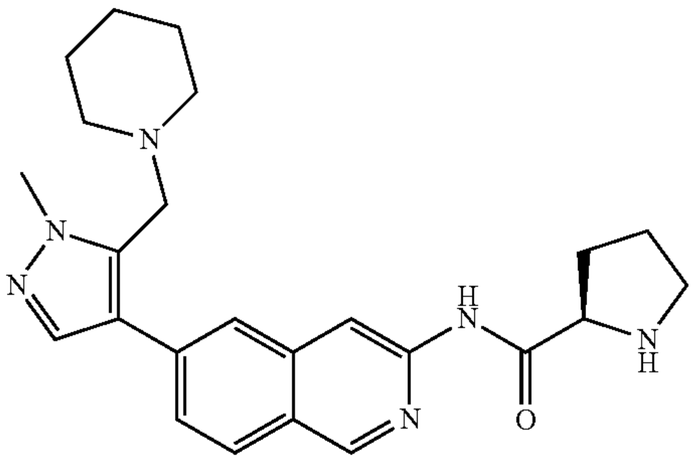
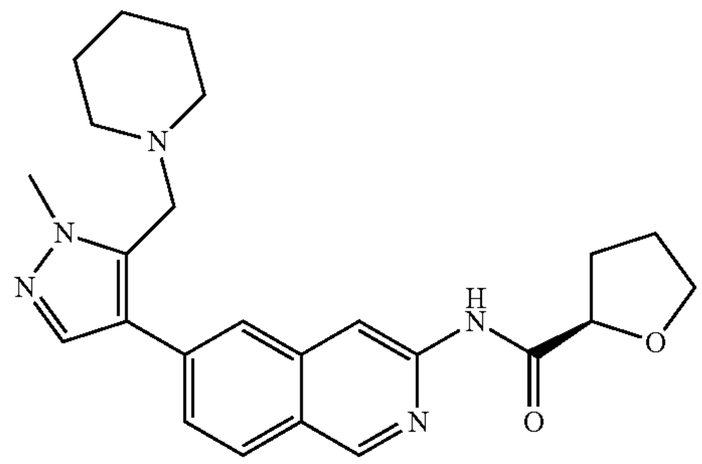
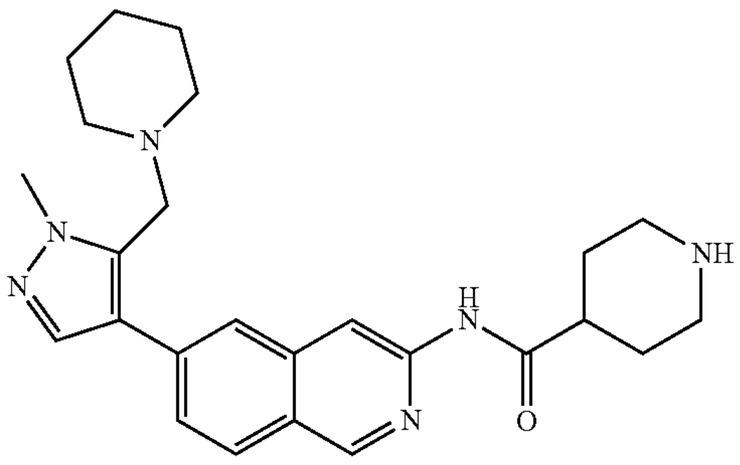
801	
802	
803	
804	
805	

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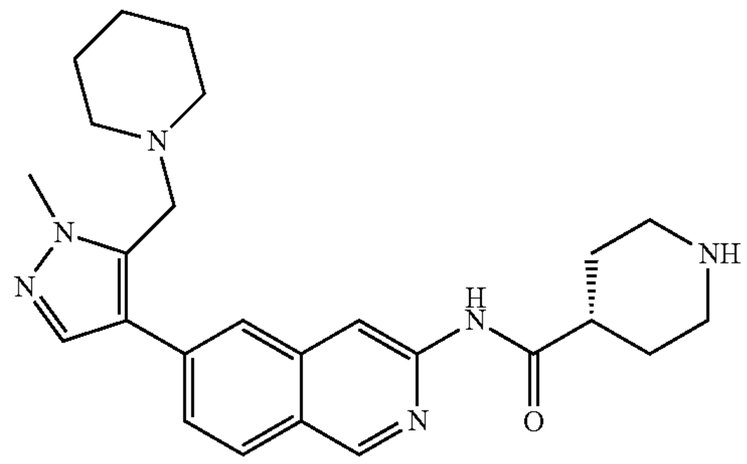
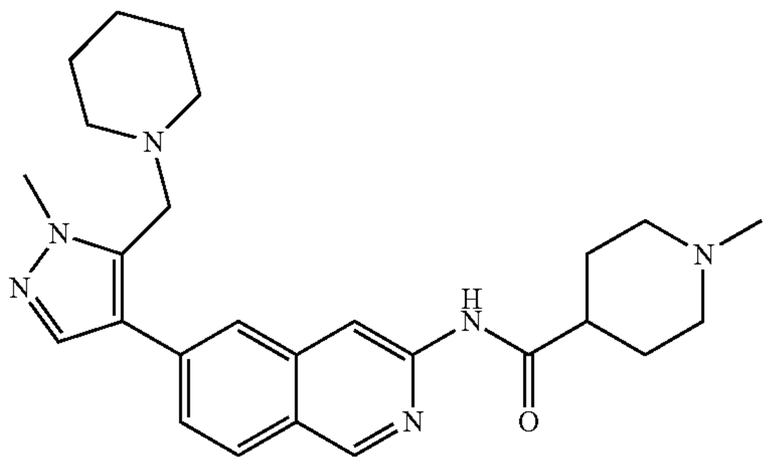
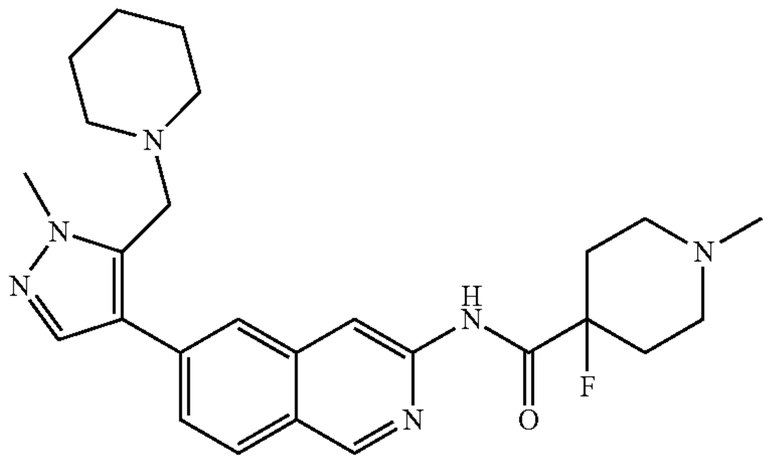
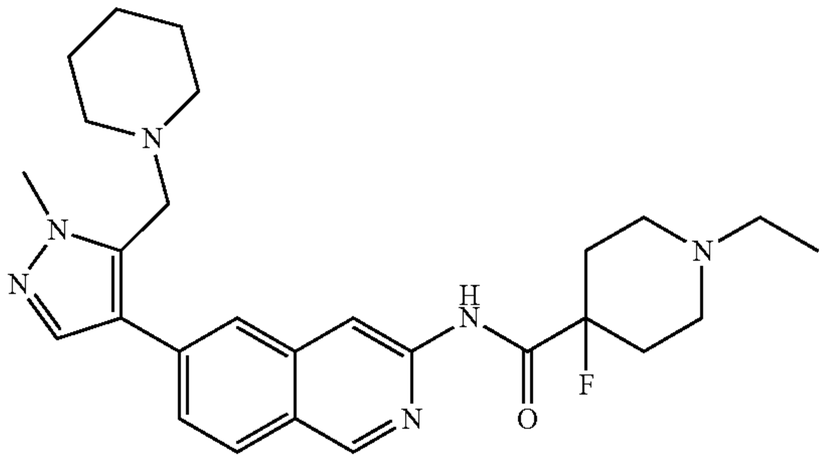
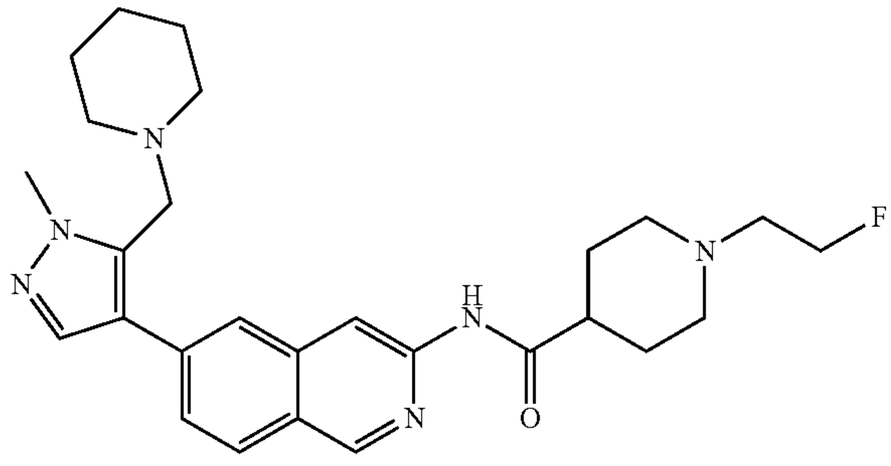
806	
807	
808	
809	
810	

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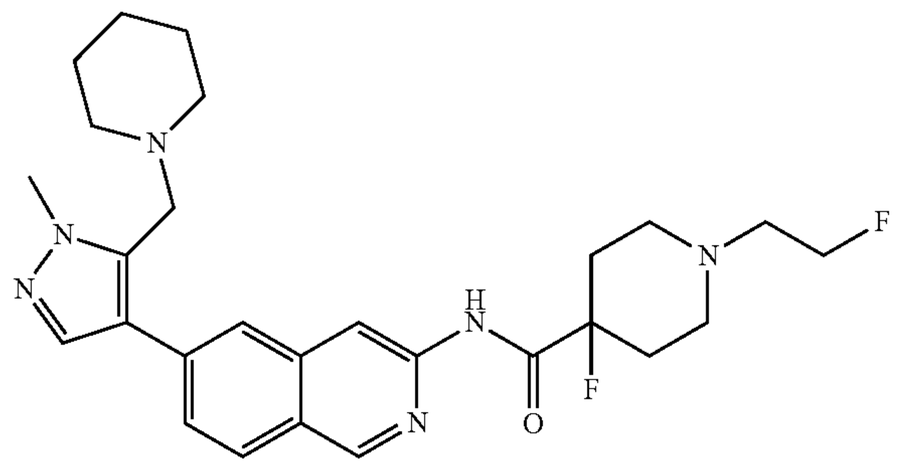
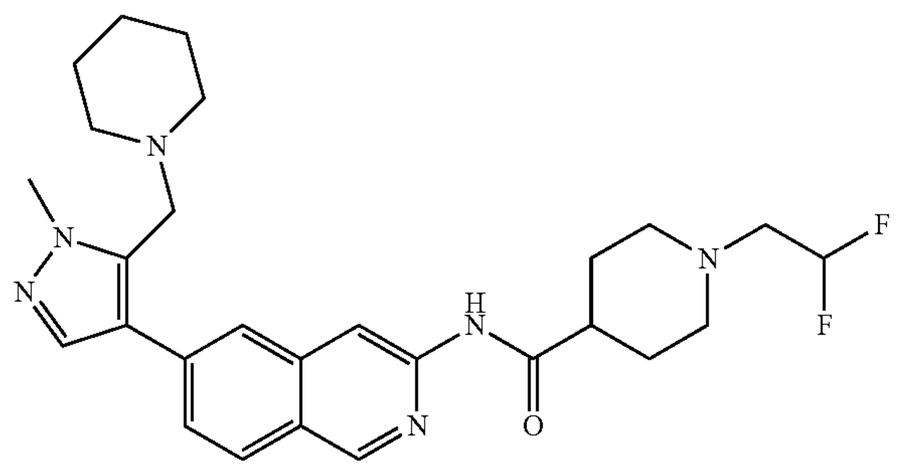
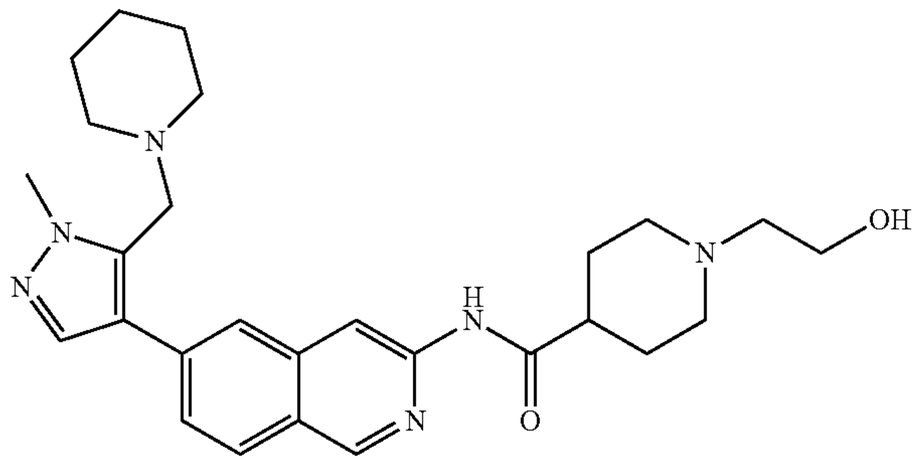
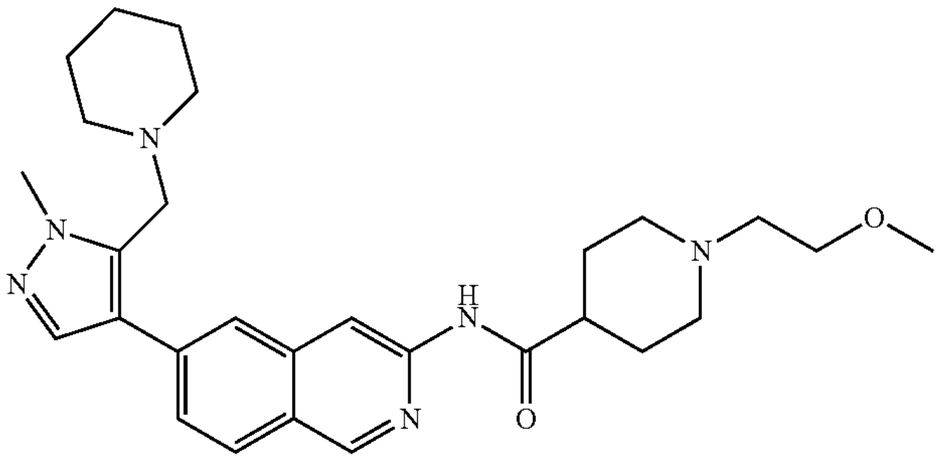
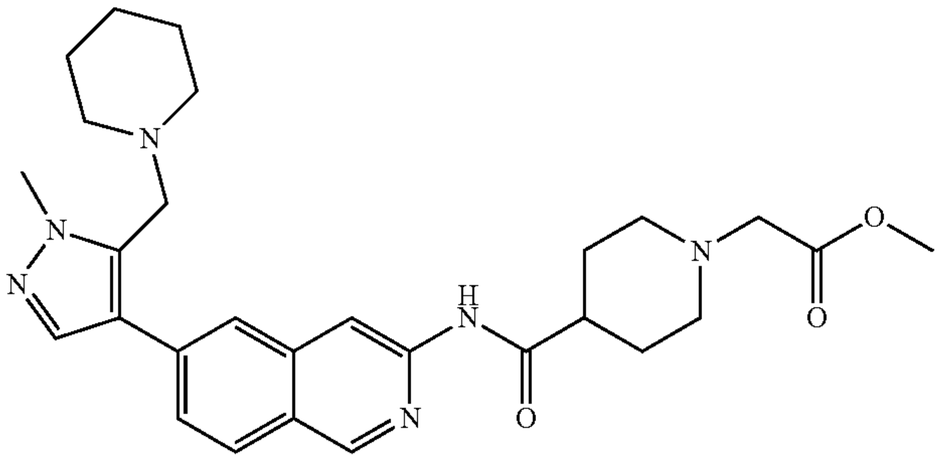
811	
812	
813	
814	
815	

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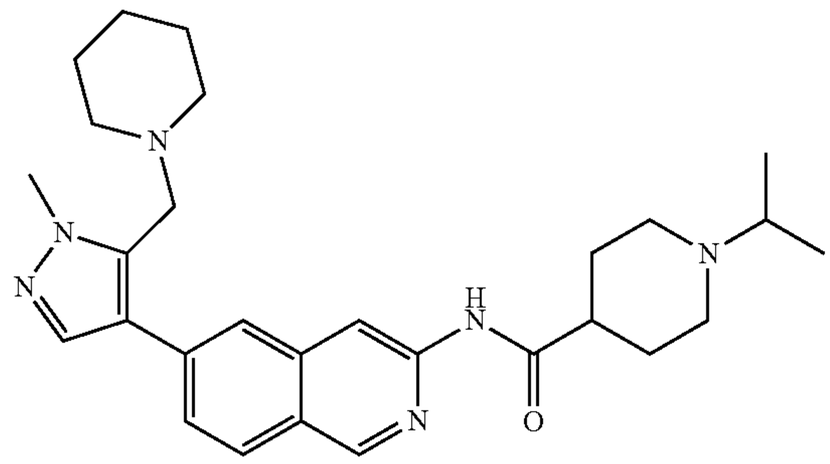

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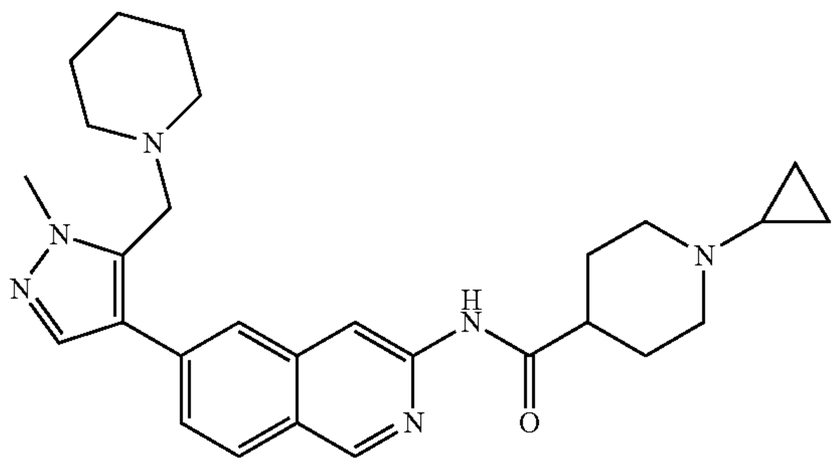

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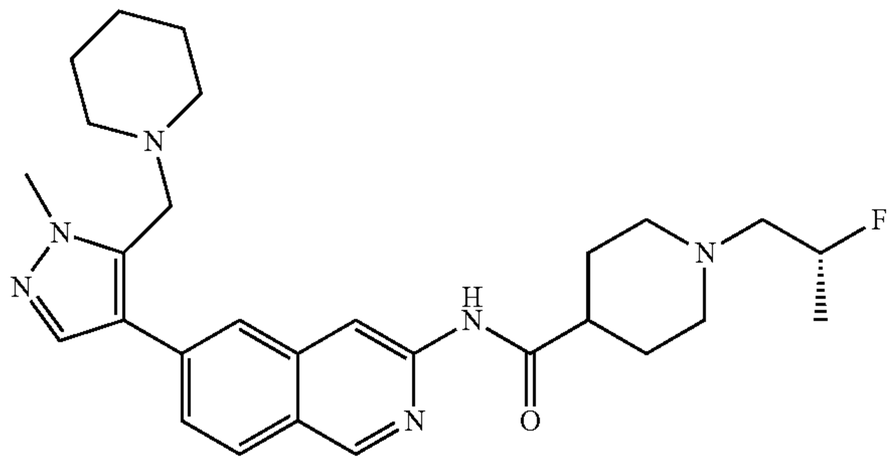

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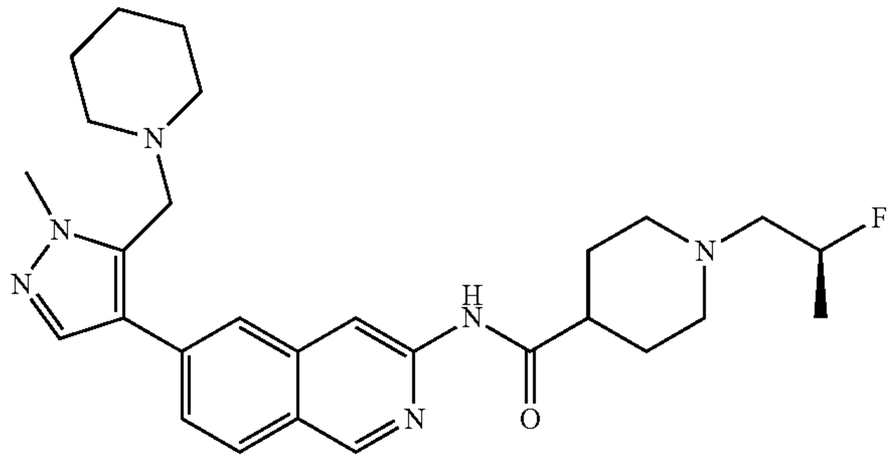

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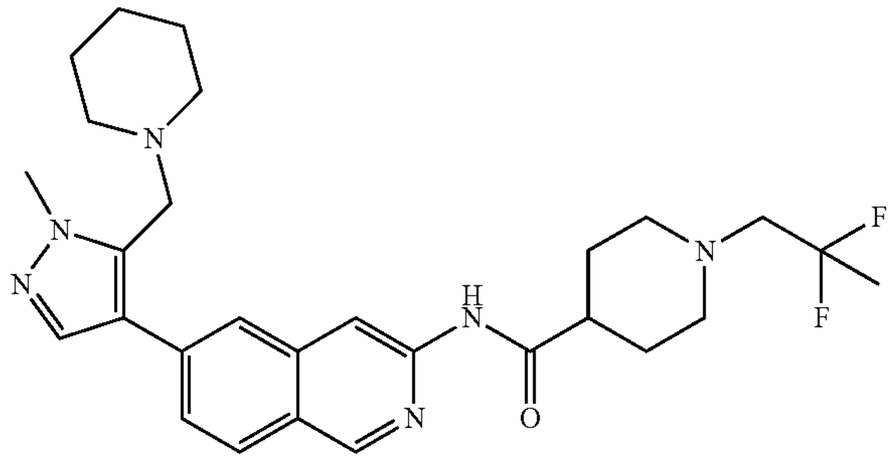

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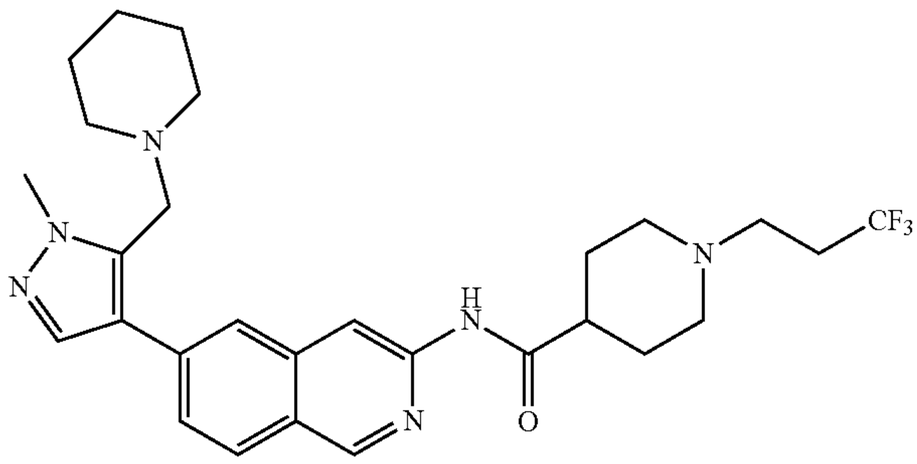
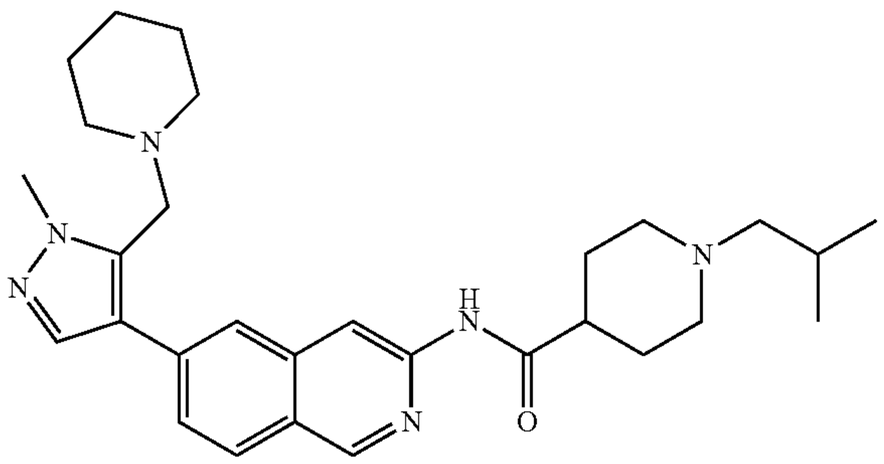
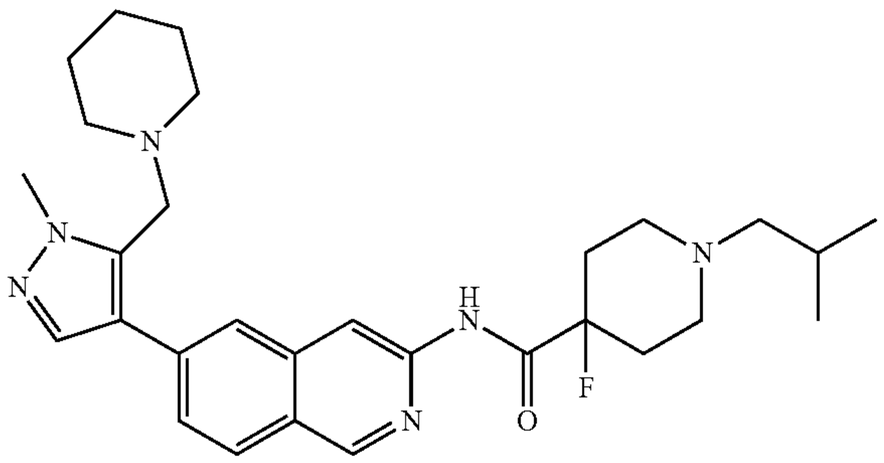
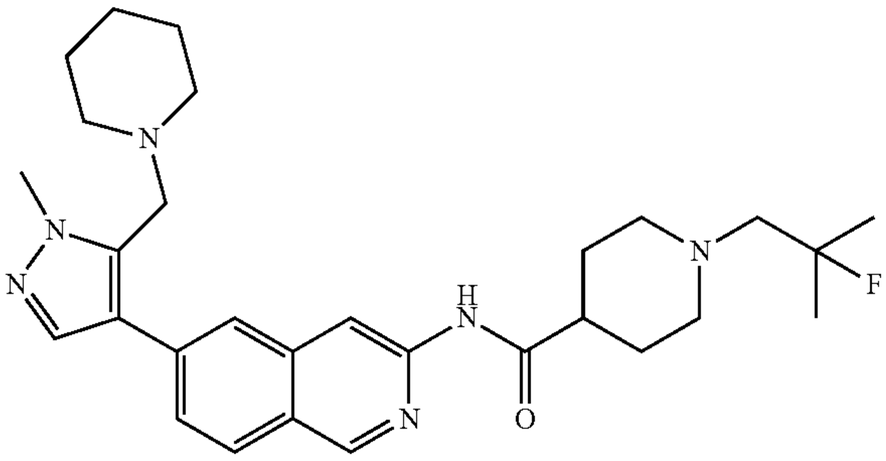
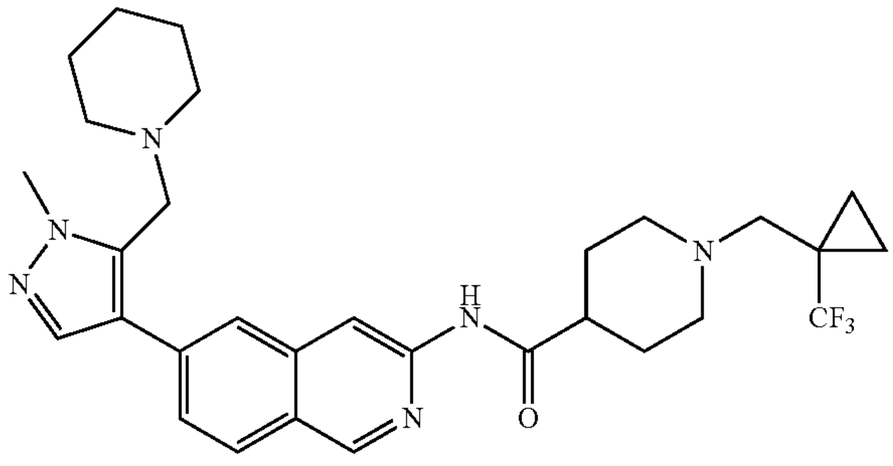
821	
822	
823	
824	
825	

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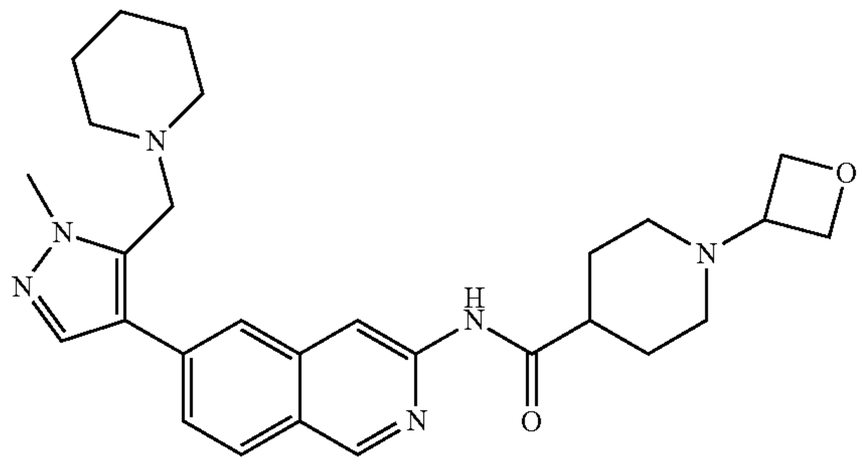

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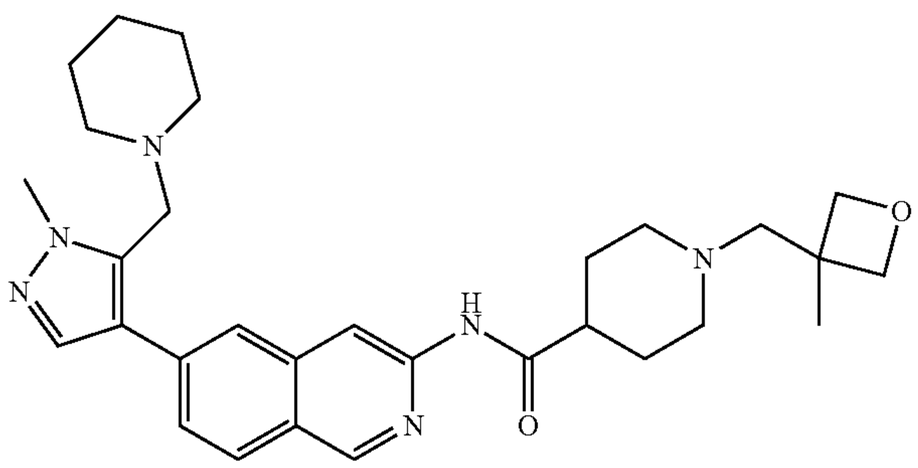

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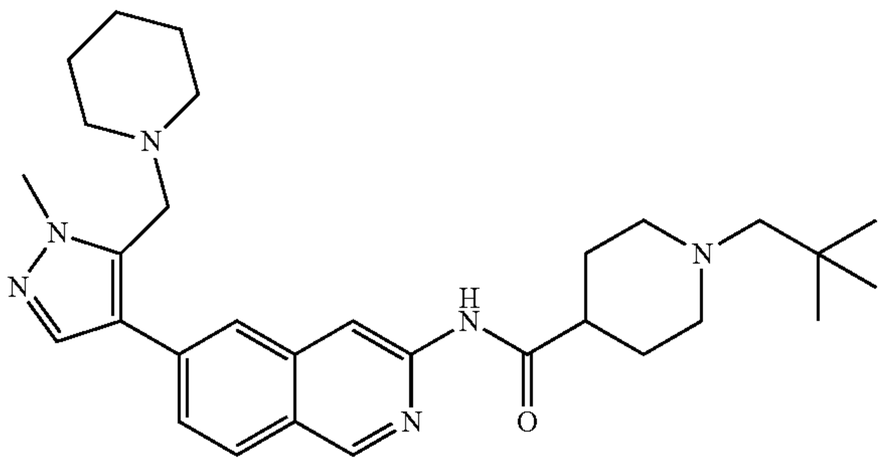

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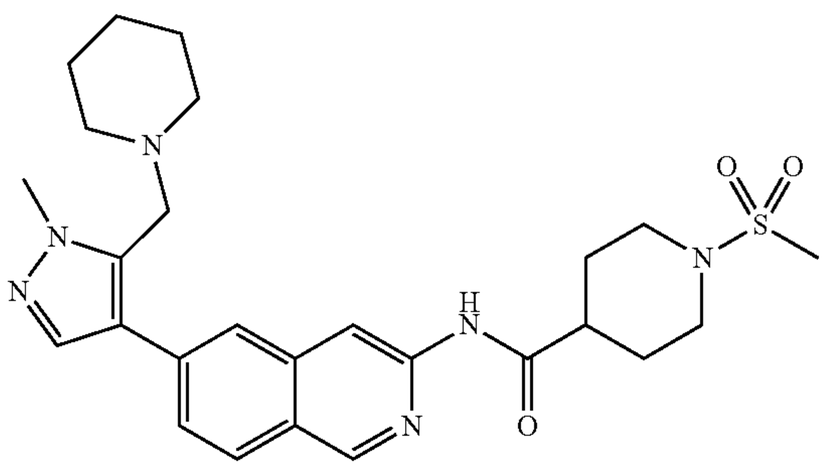

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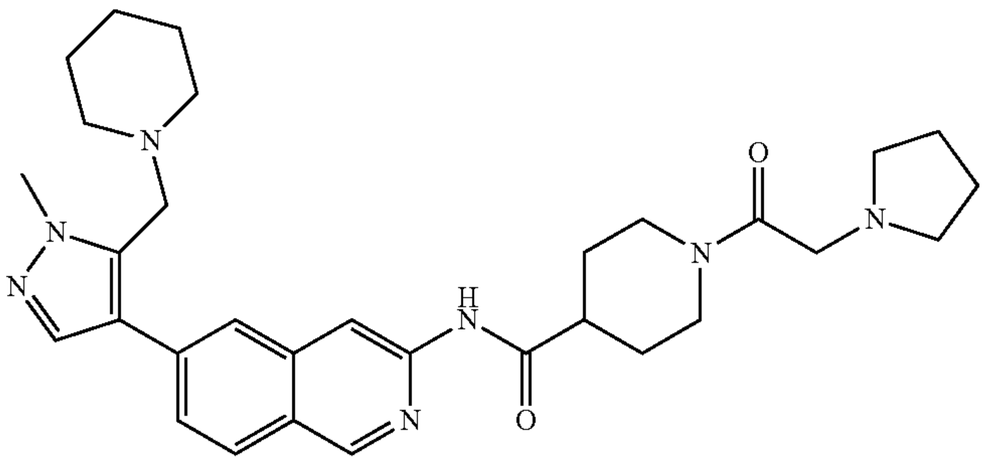

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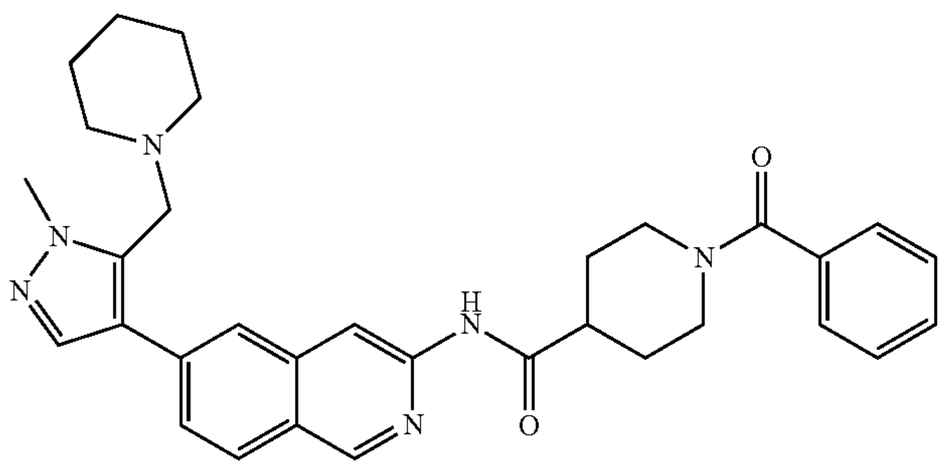
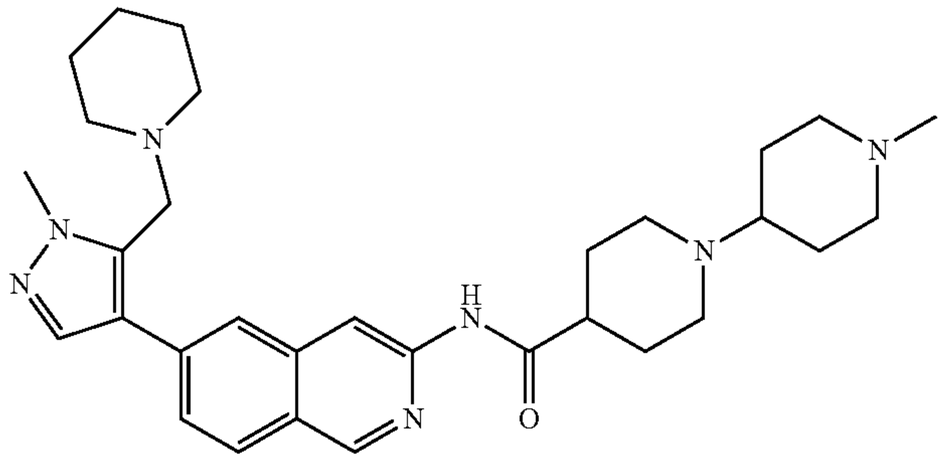
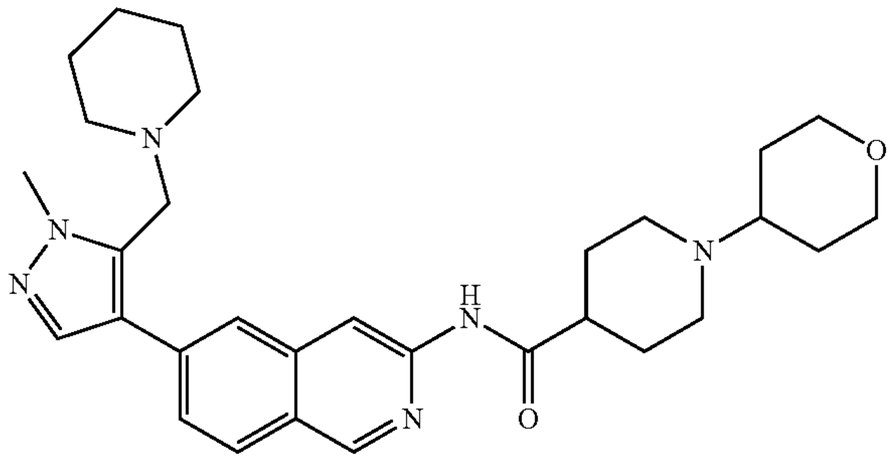
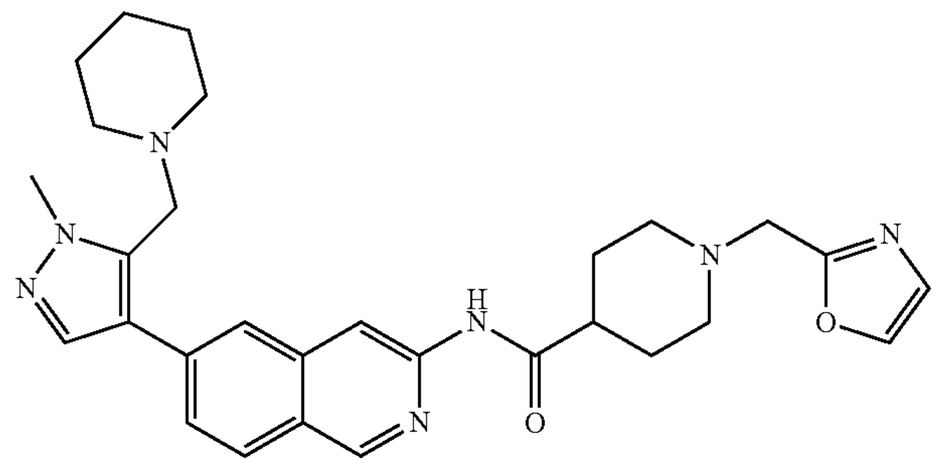
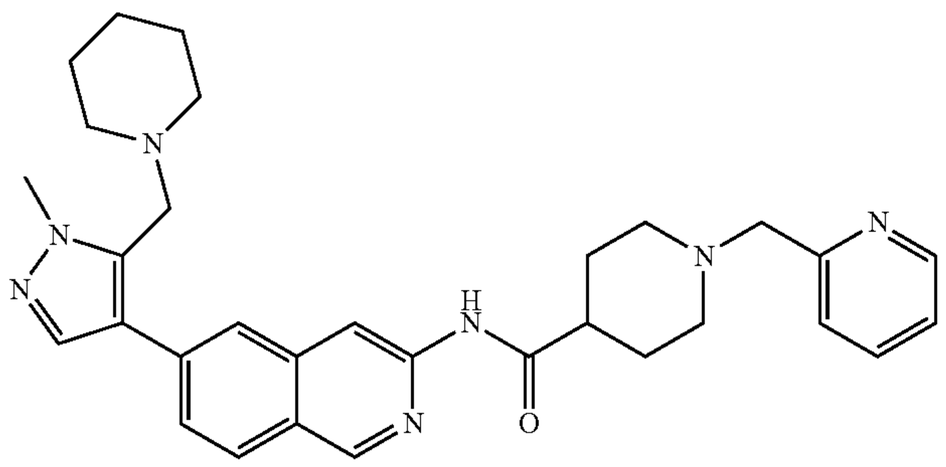
831	
832	
833	
834	
835	

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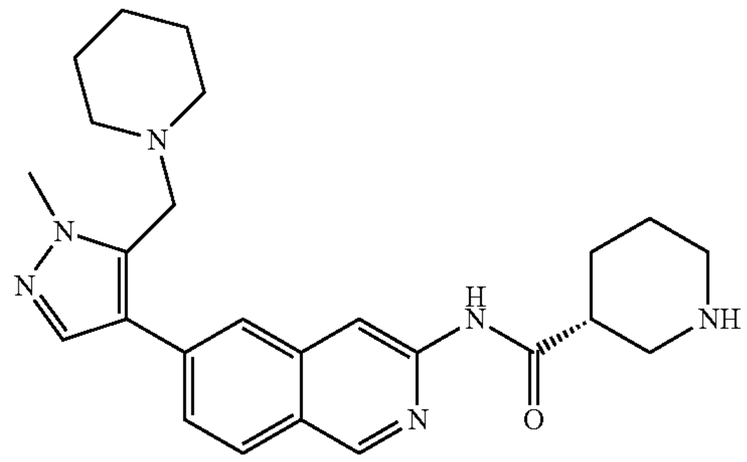

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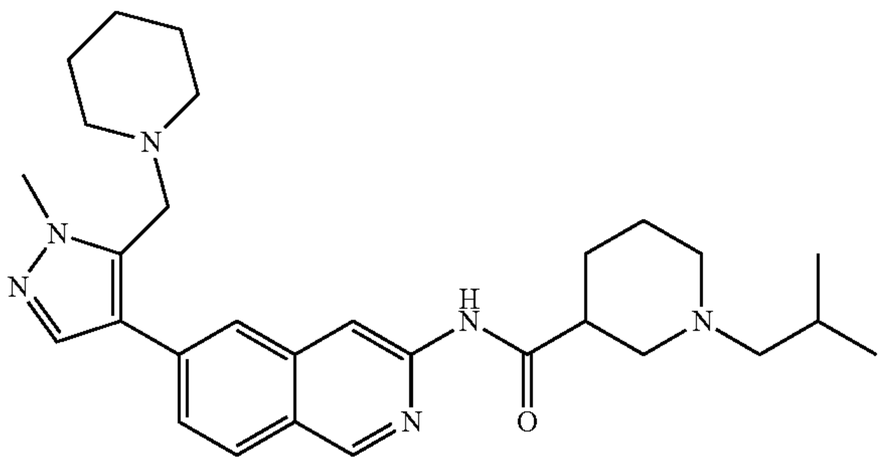

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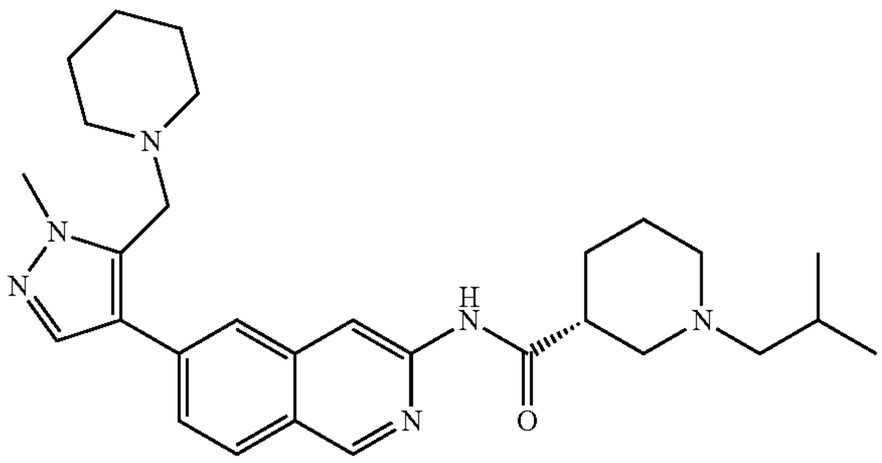

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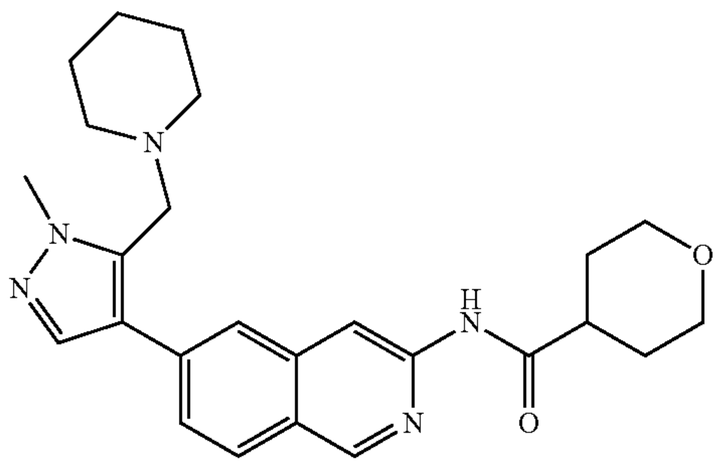

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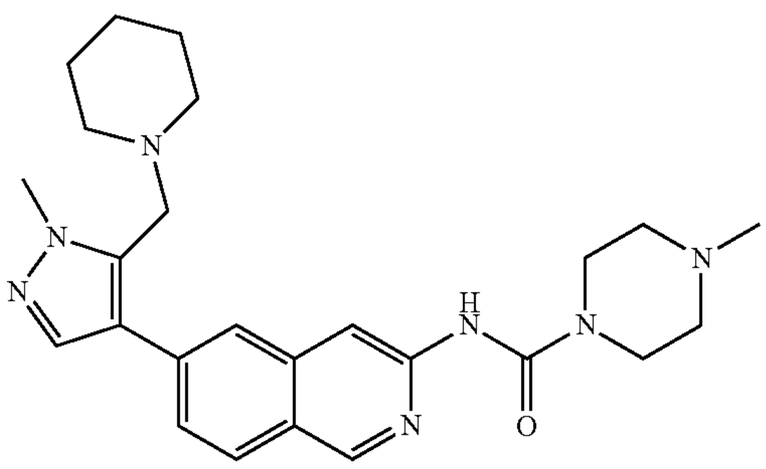

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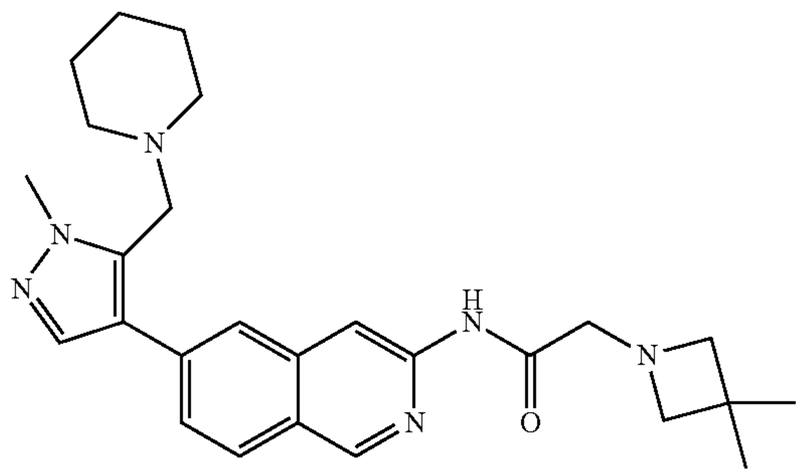
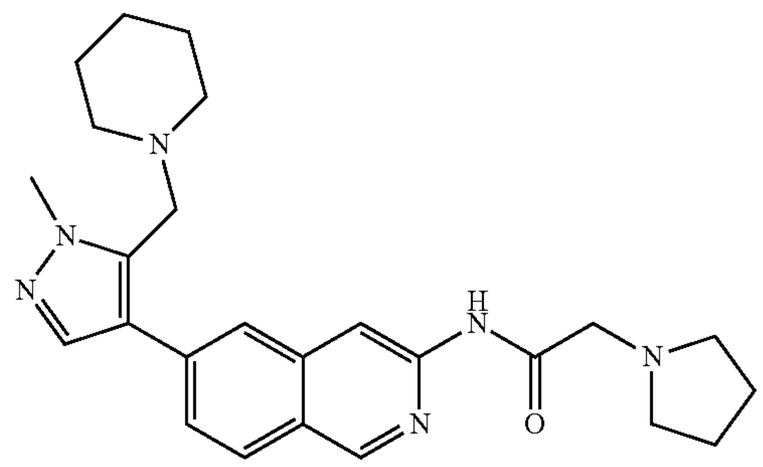
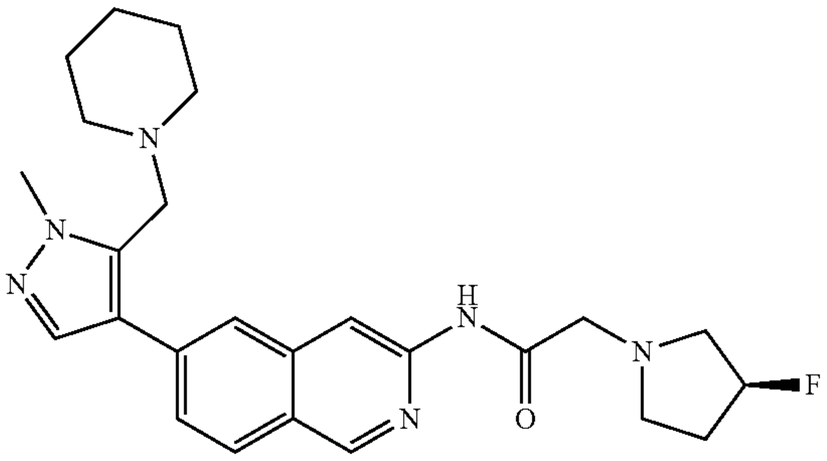
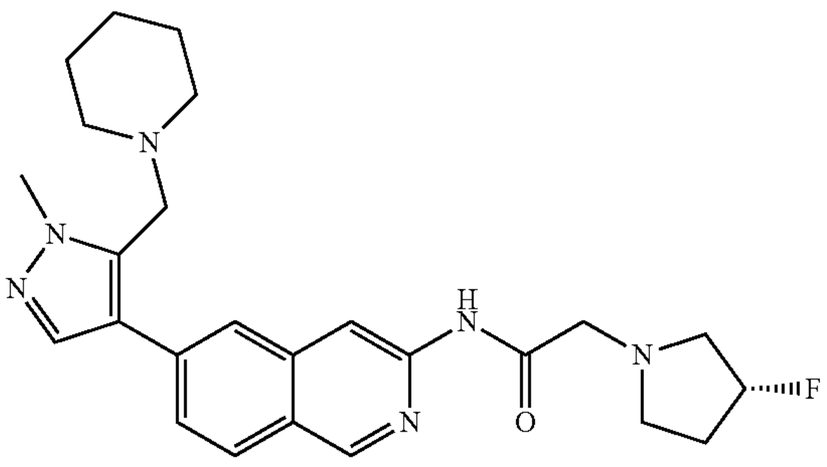
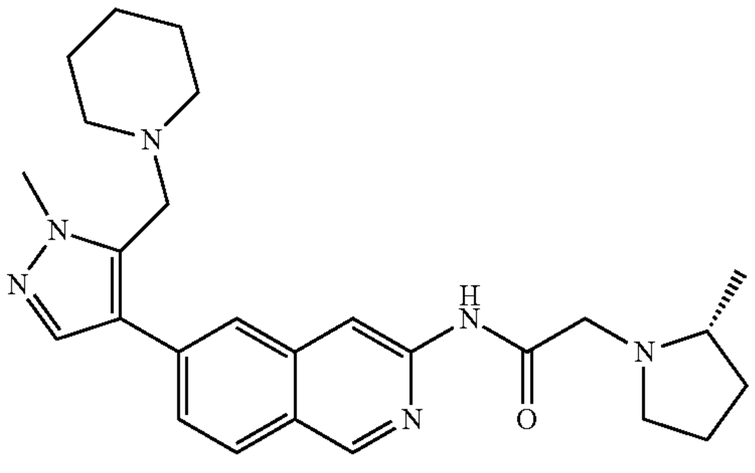
841	
842	
843	
844	
845	

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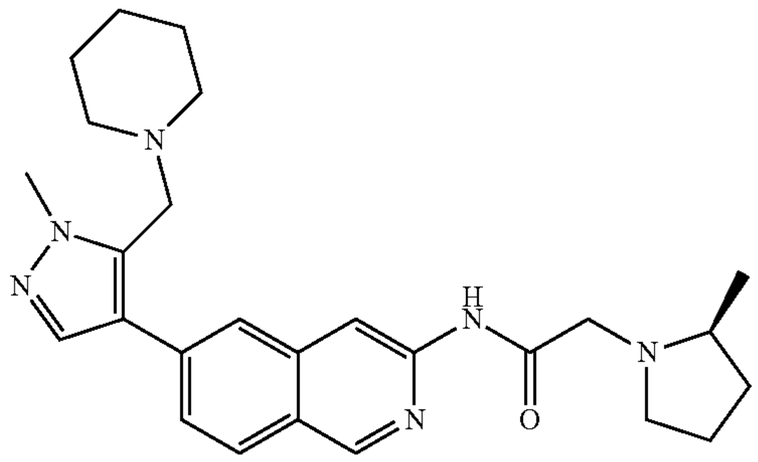
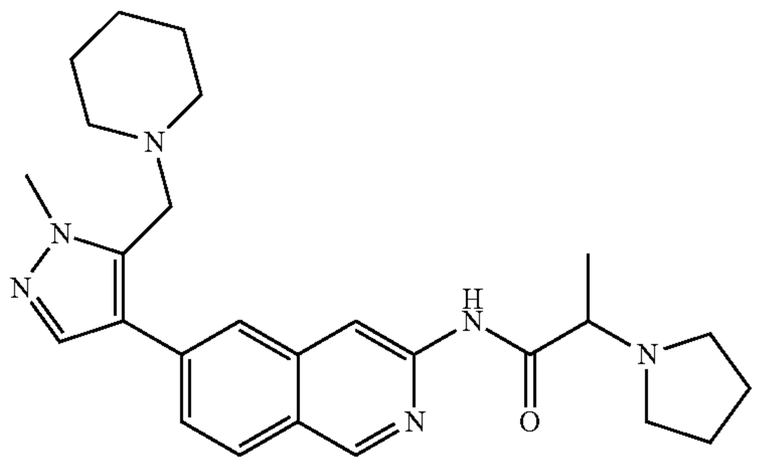
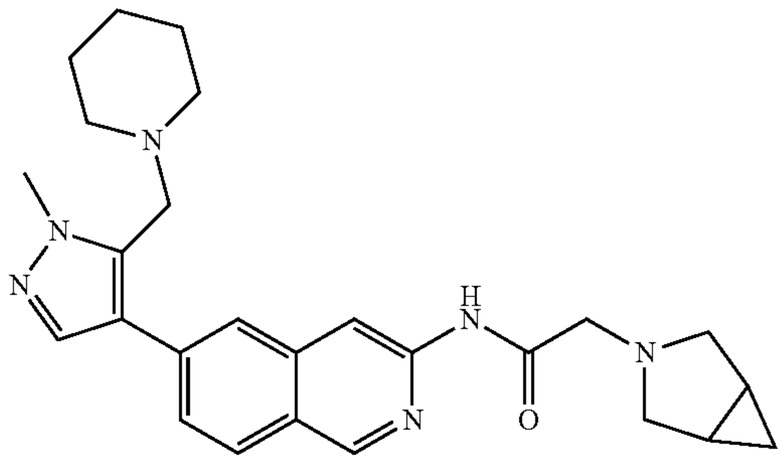
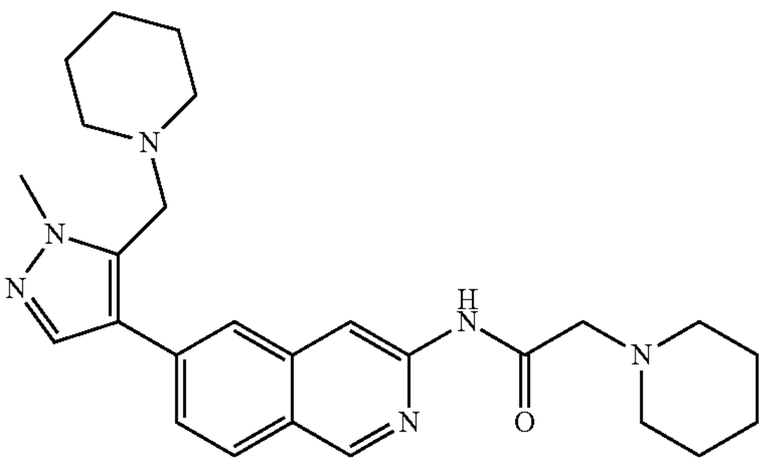
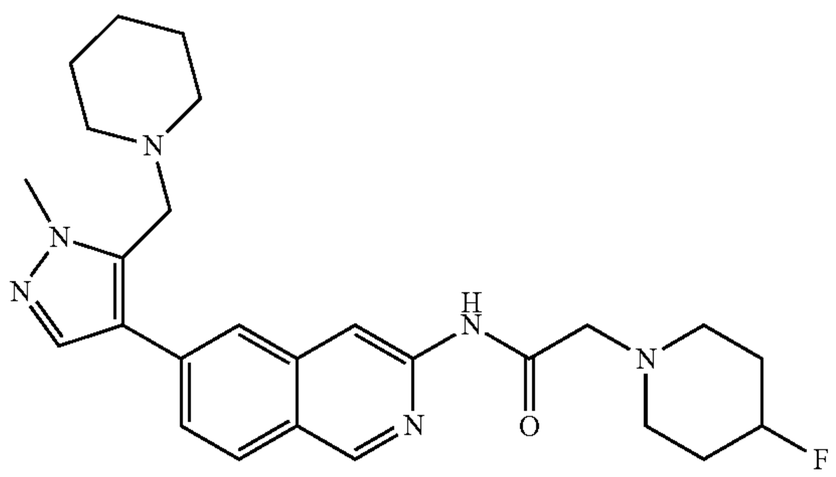
846	
847	
848	
849	
850	

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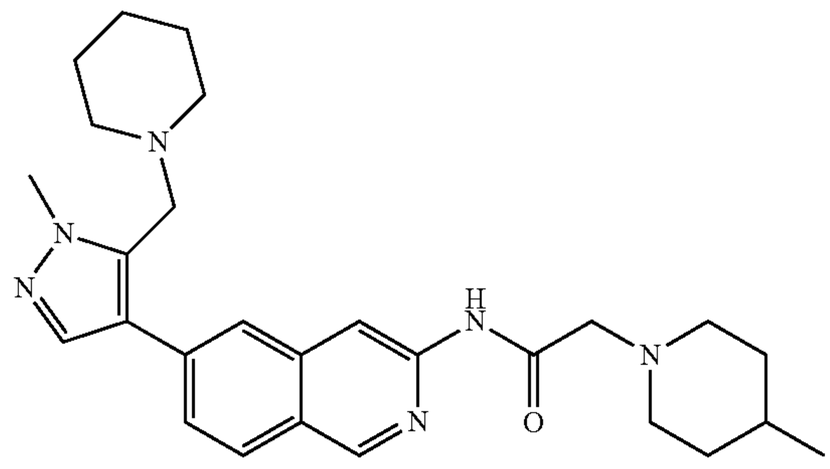
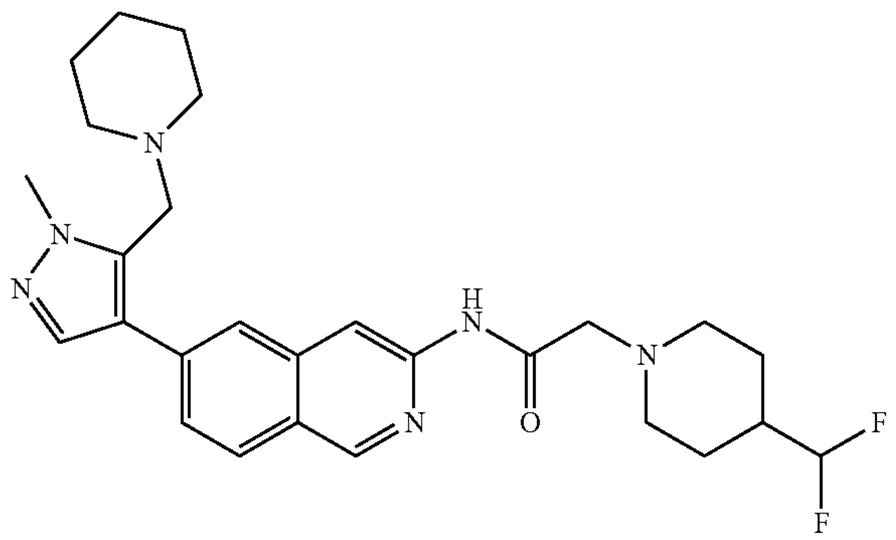
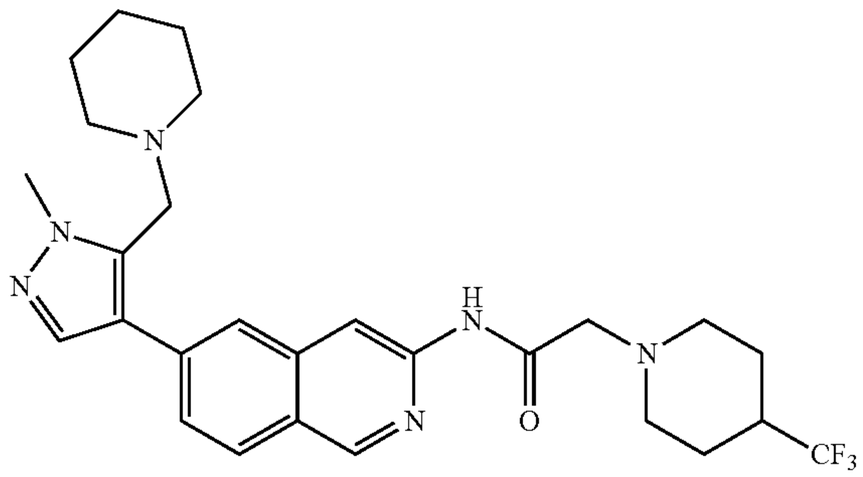
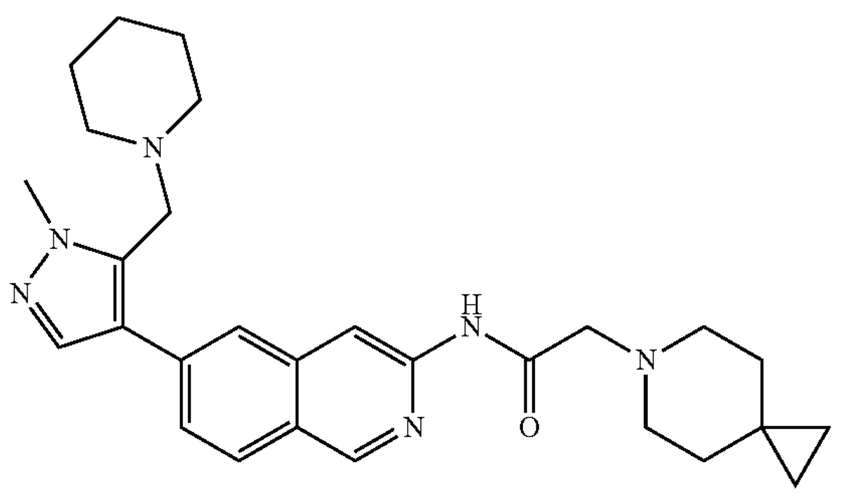
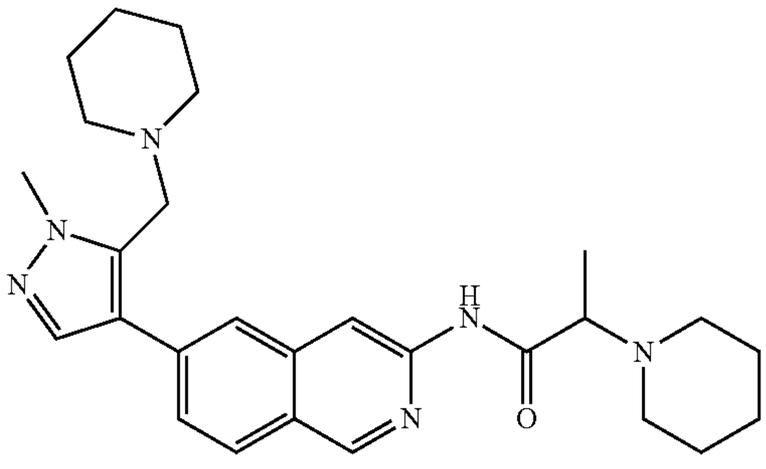
851	
852	
853	
854	
855	

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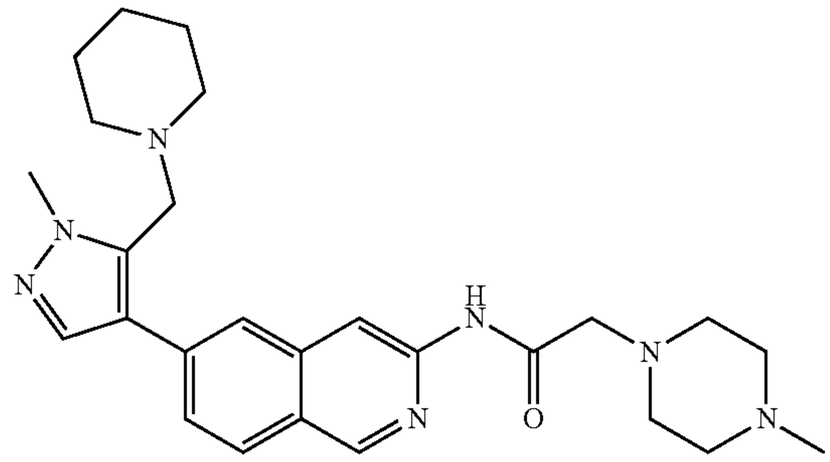
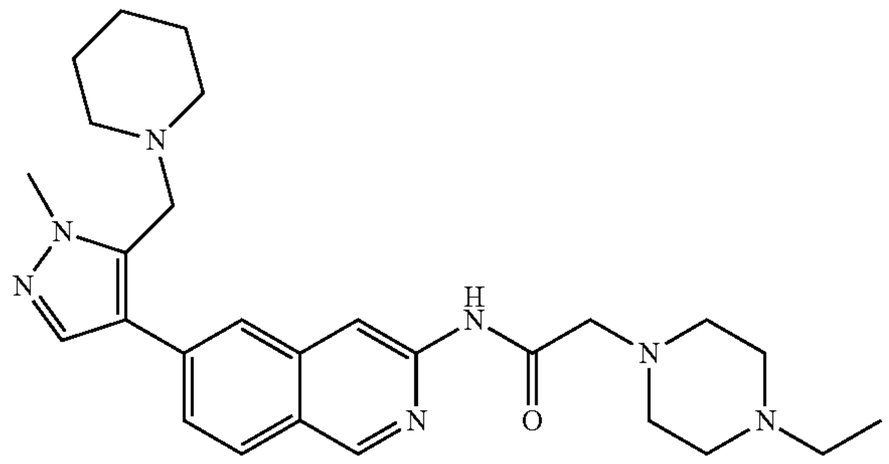
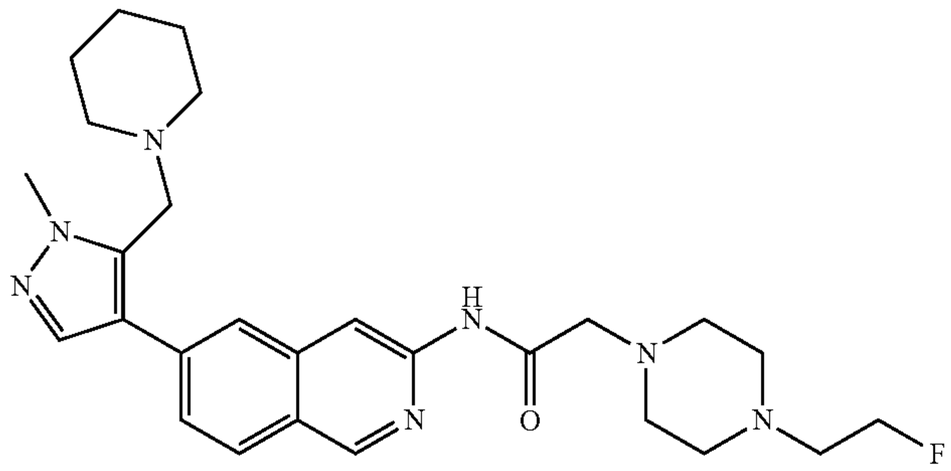
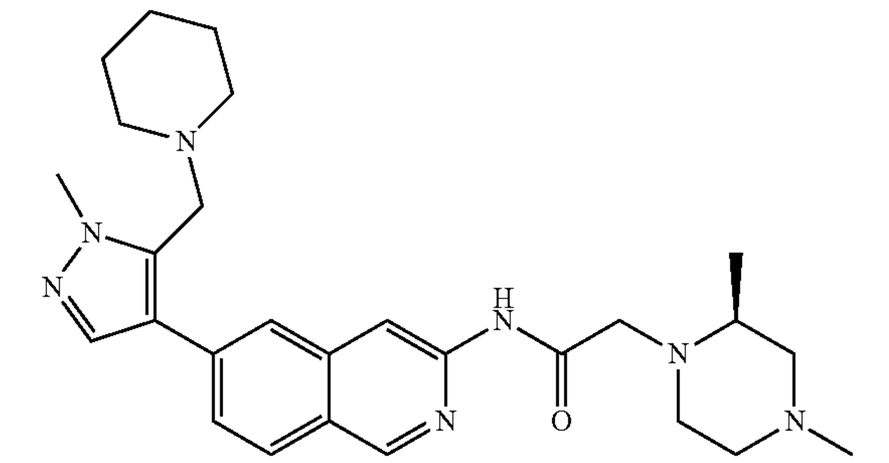
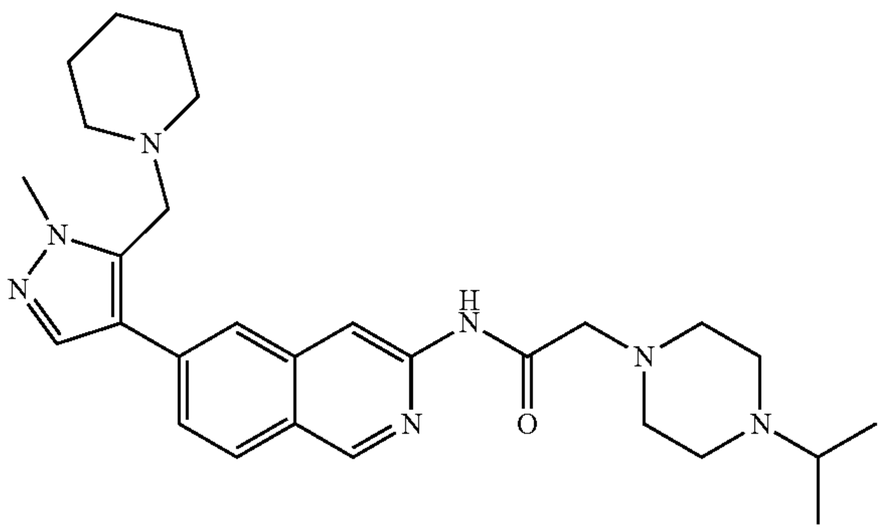
856	
857	
858	
859	
860	

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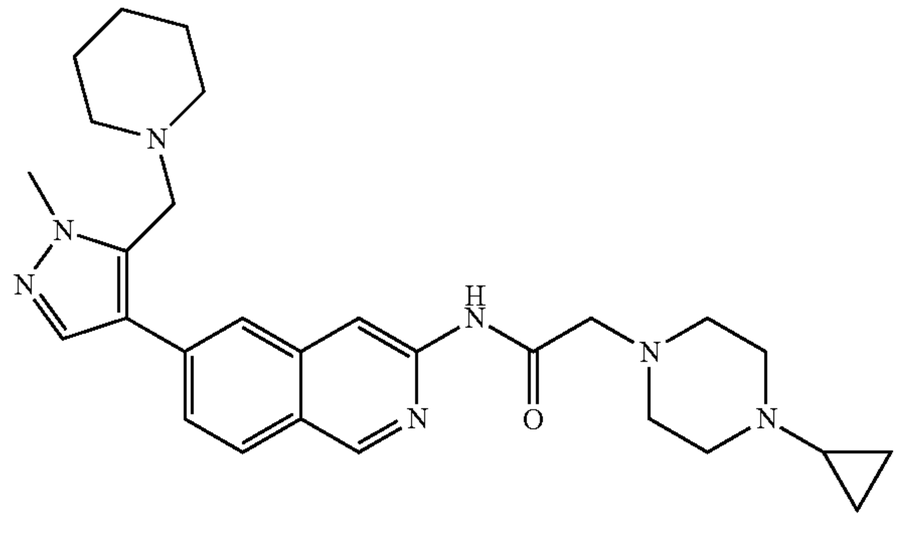
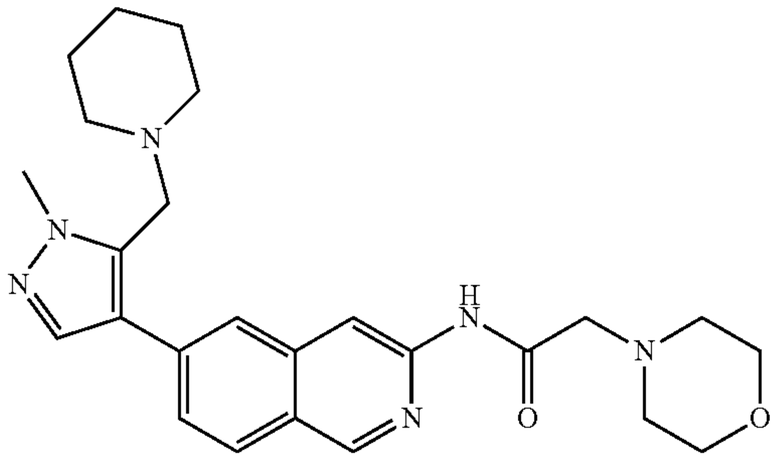
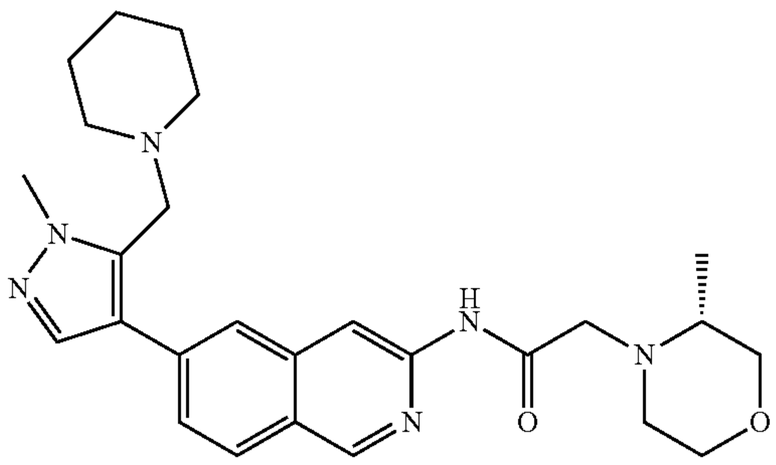
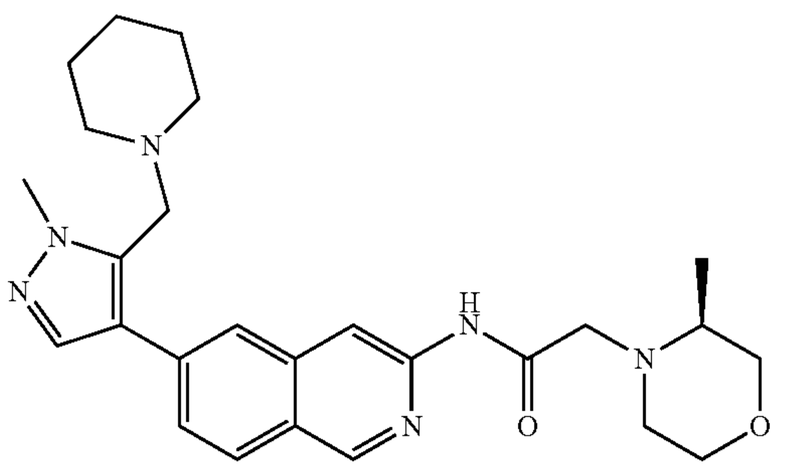
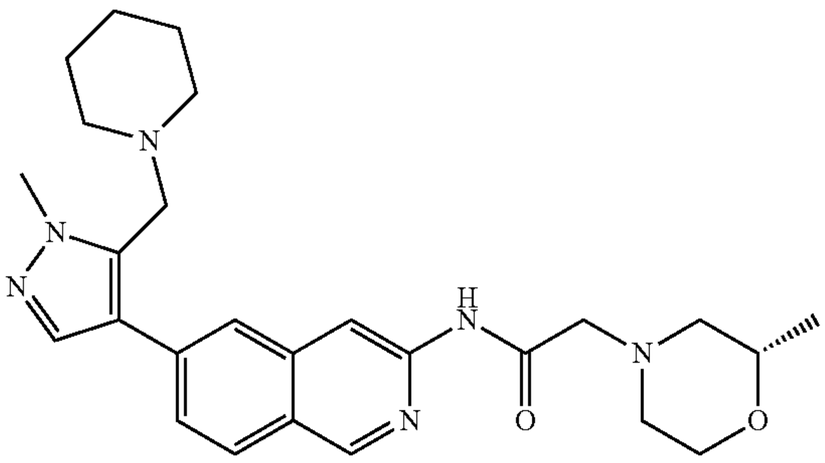
861	
862	
863	
864	
865	

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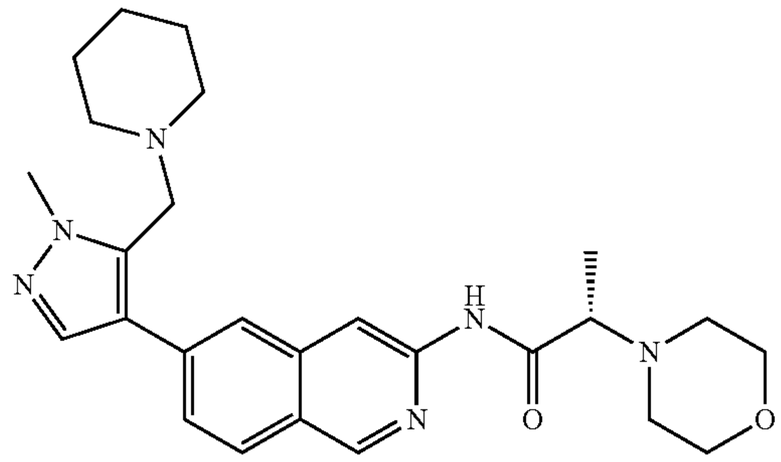

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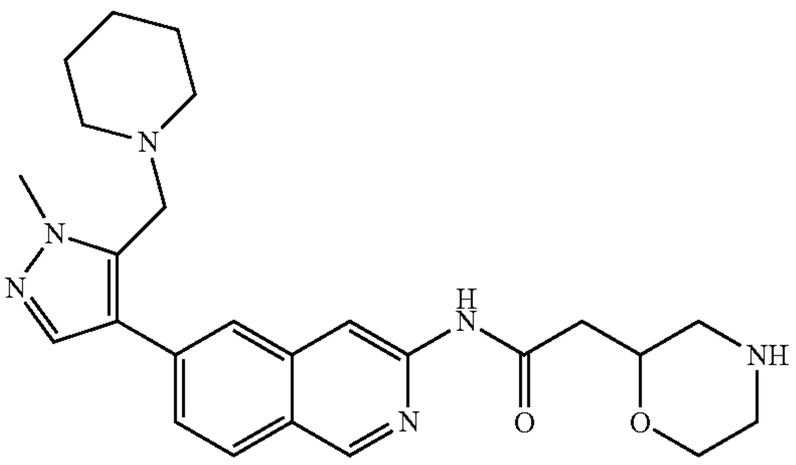

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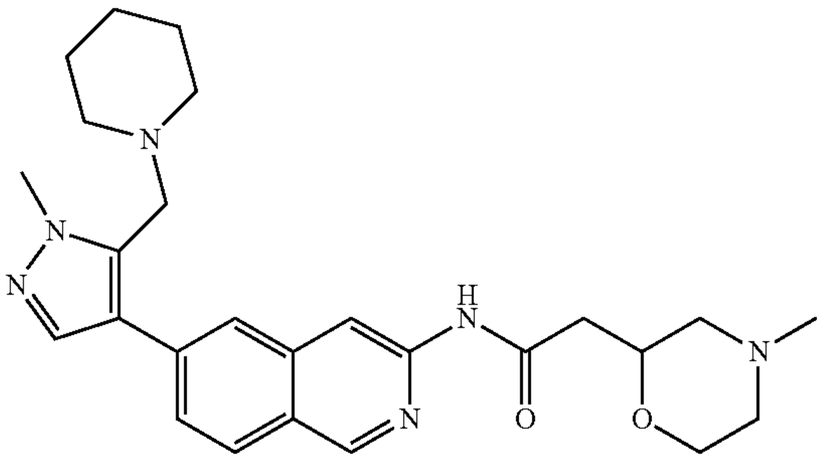

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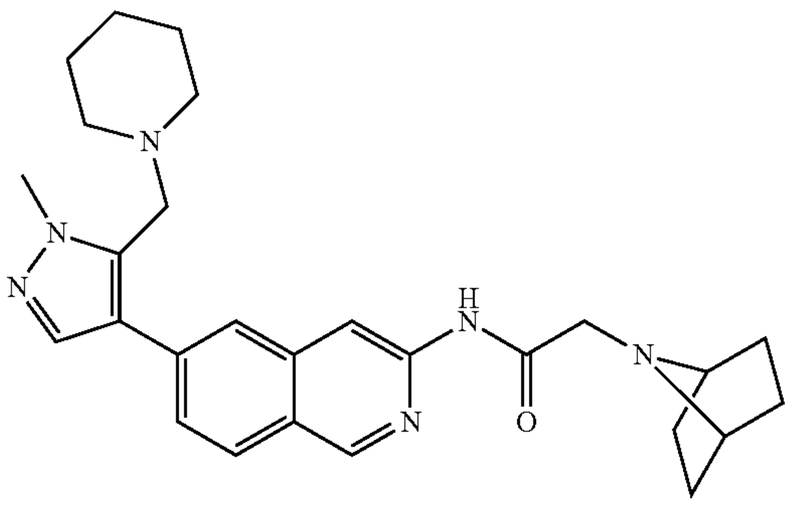

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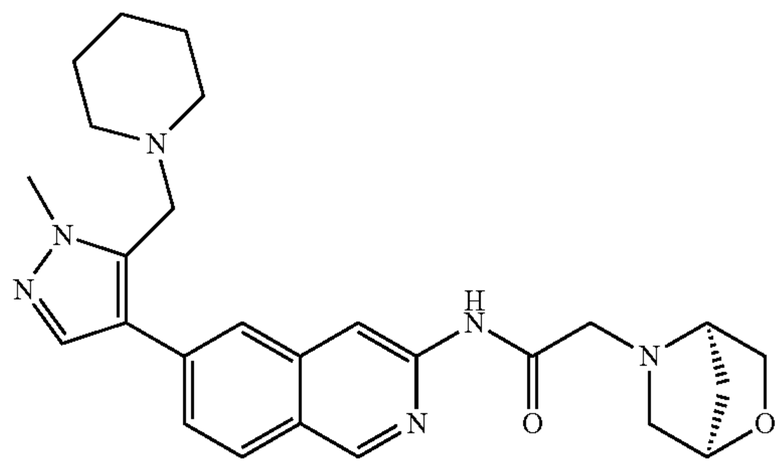

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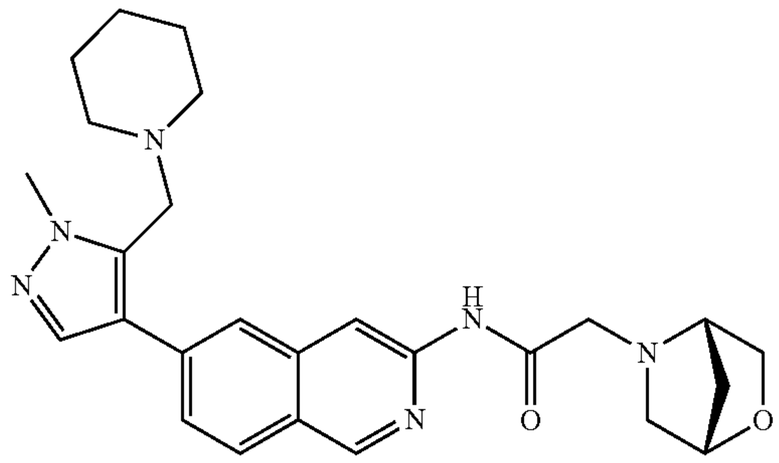

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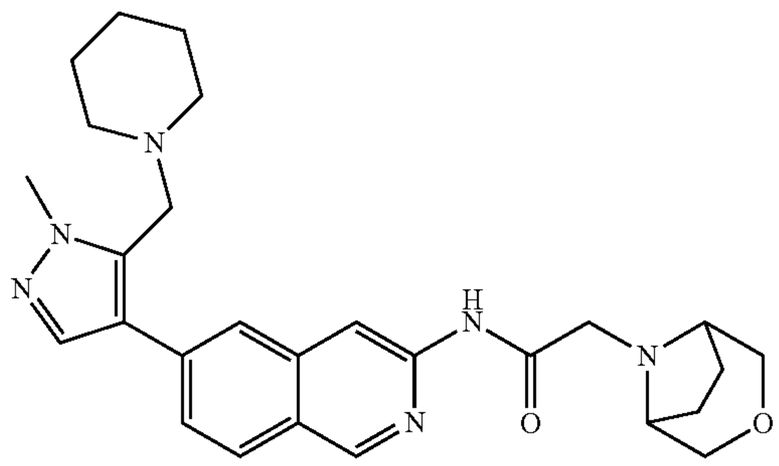

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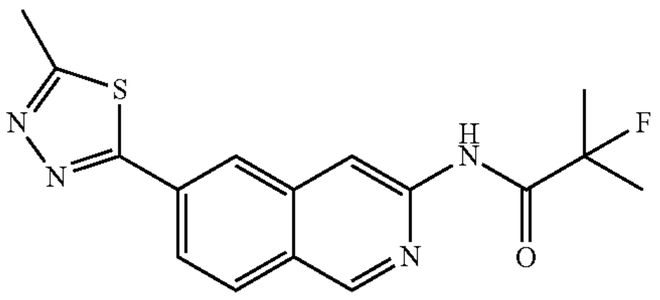

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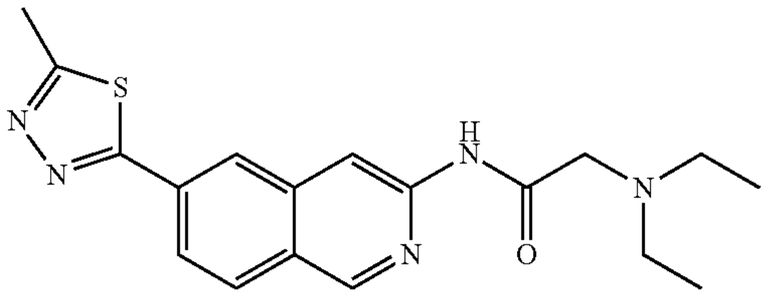

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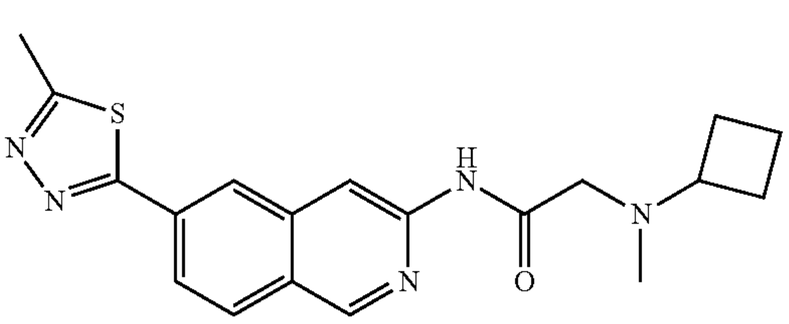

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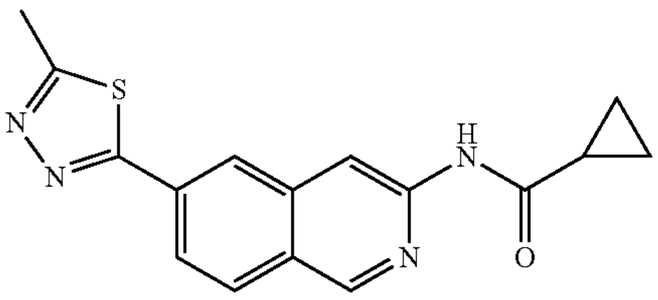

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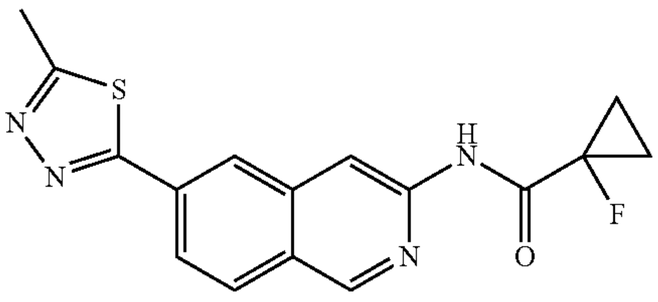

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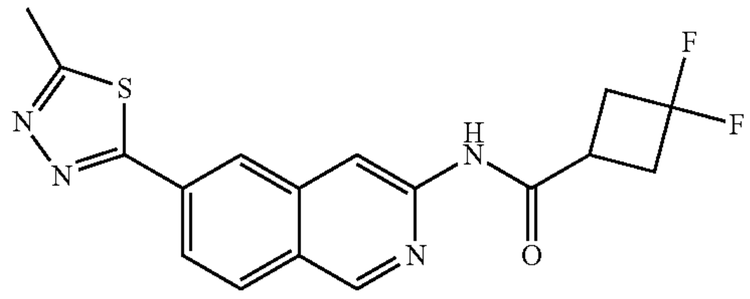
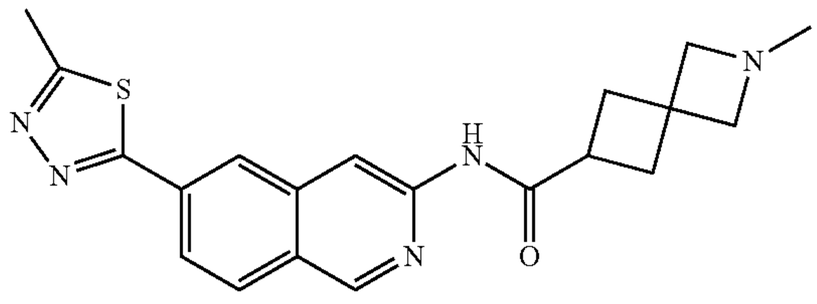
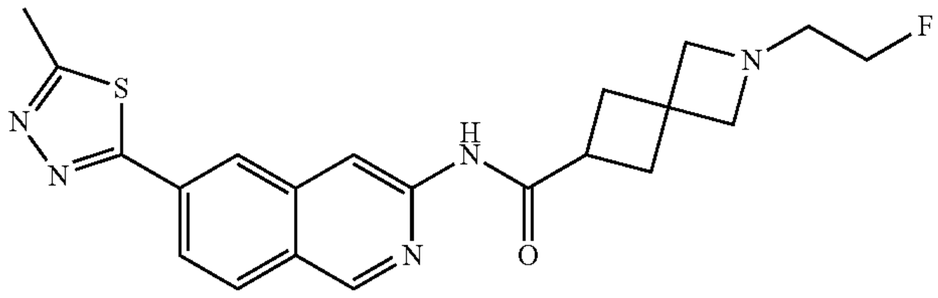
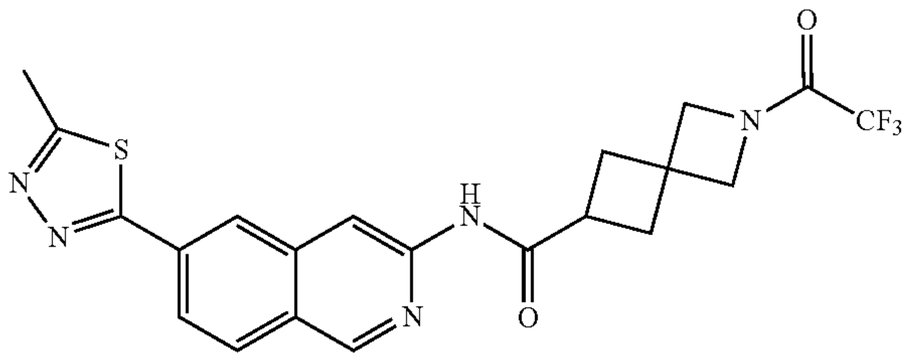
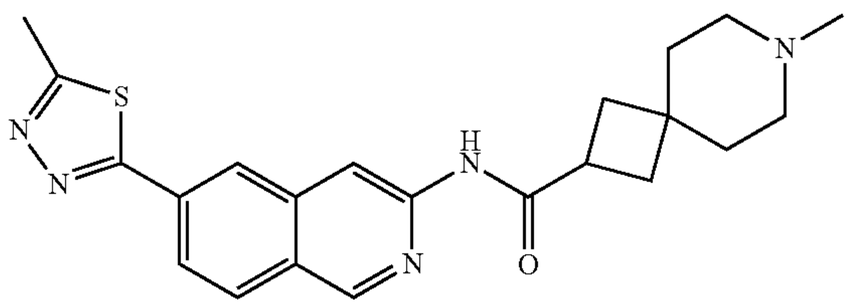
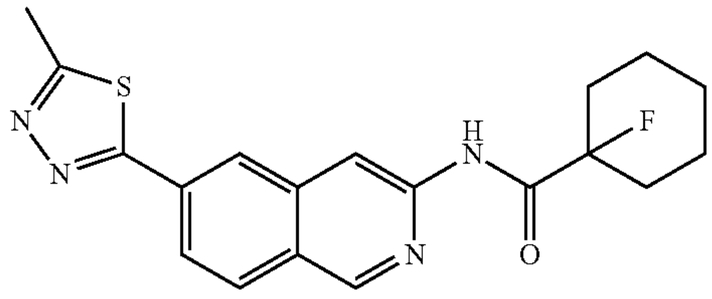
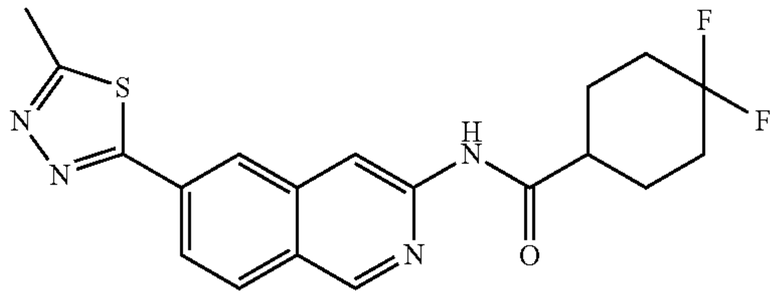
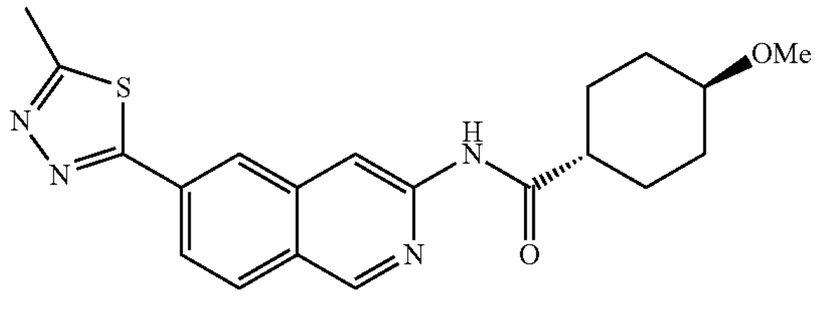
	878
	879
	880
	881
	882
	883
	884
	885

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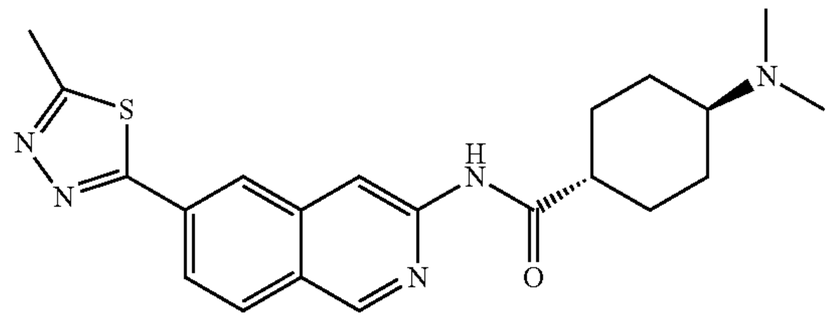
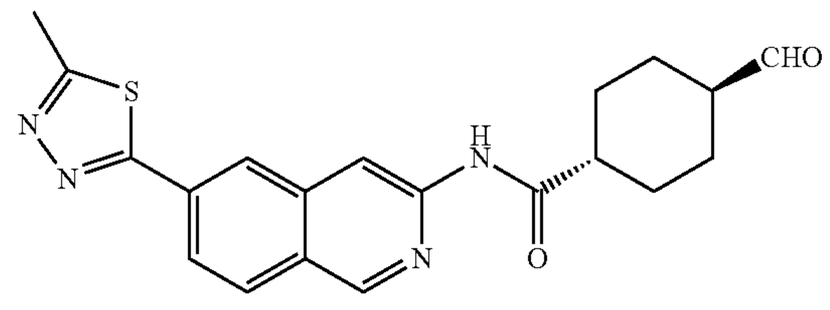
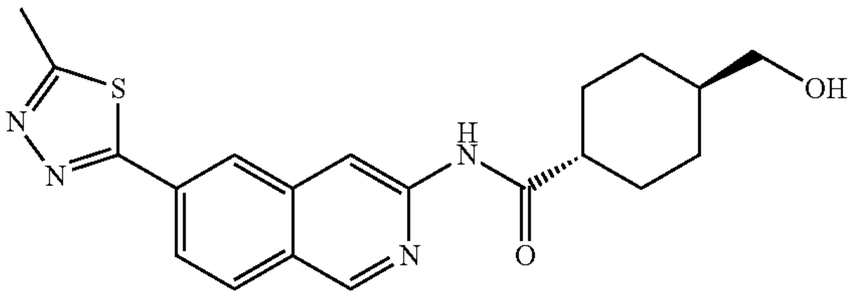
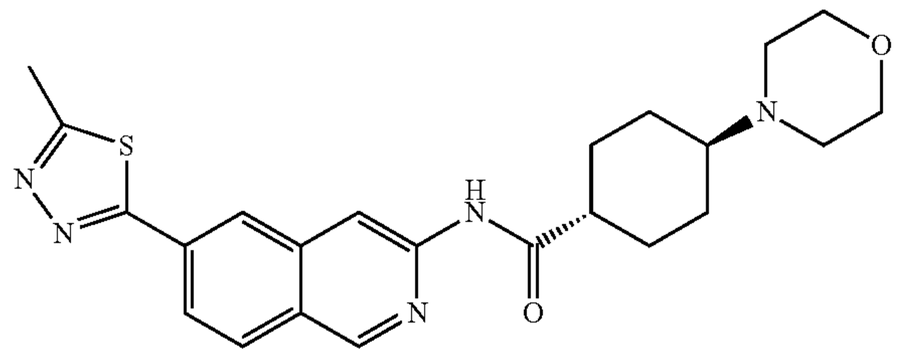
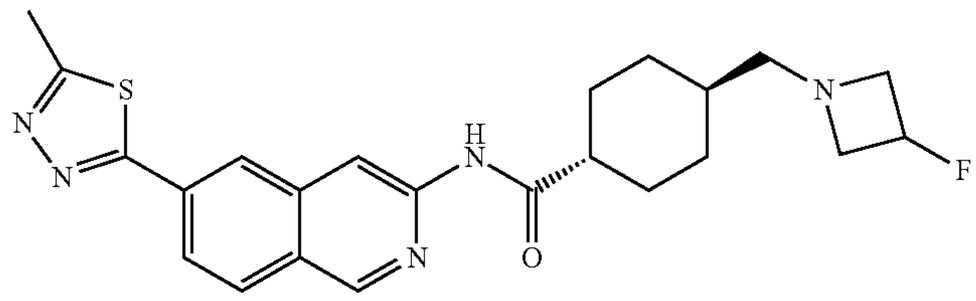
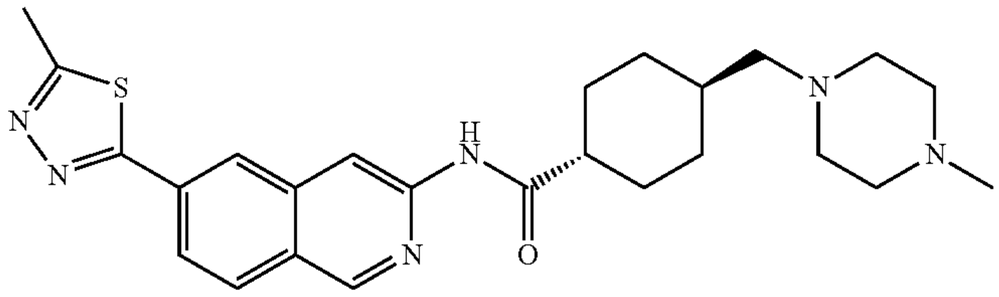
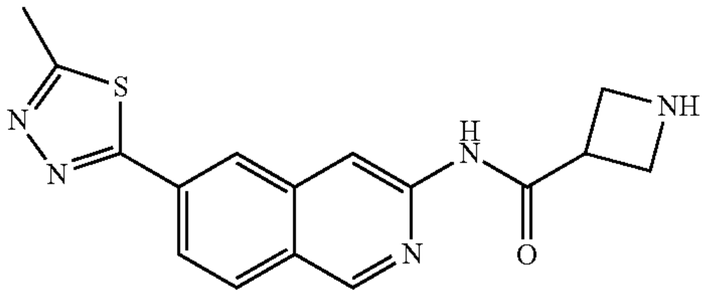
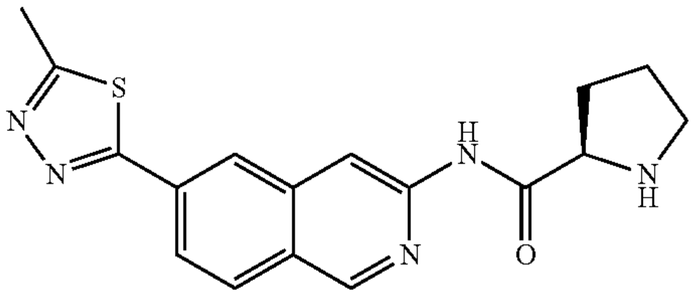
	886
	887
	888
	889
	890
	891
	892
	893

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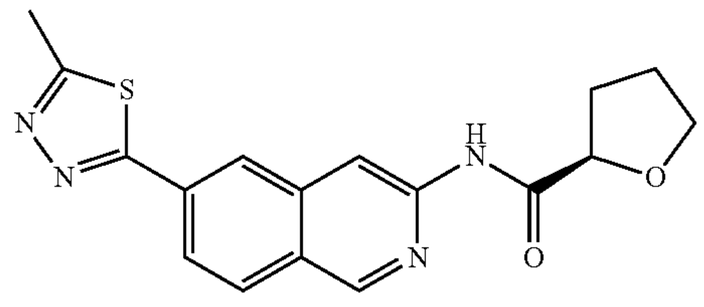
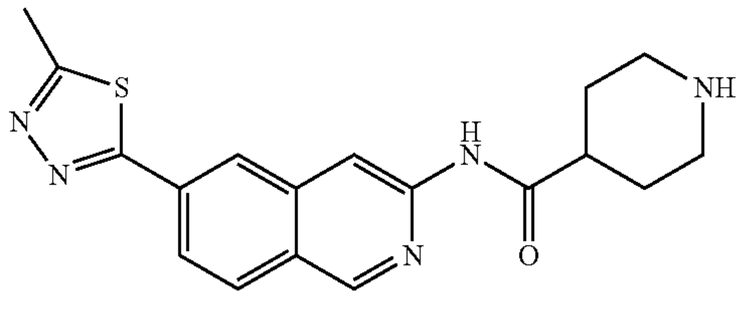
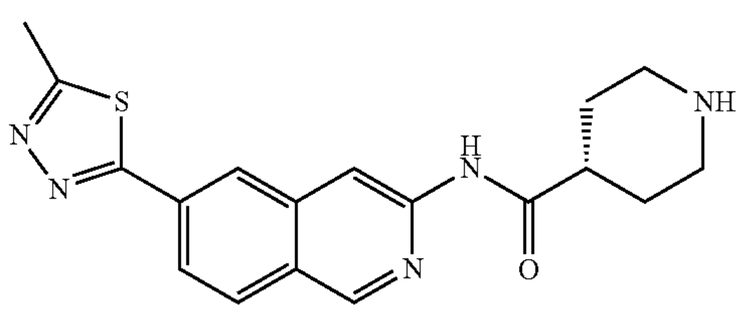
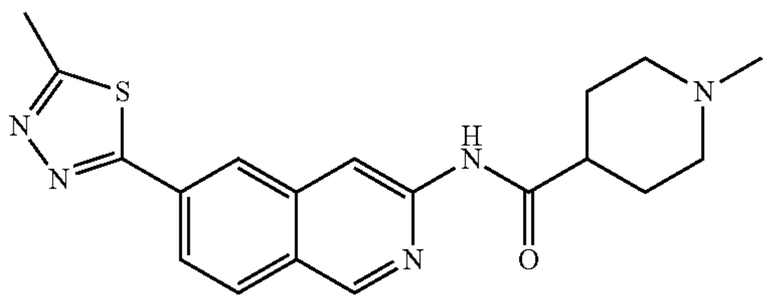
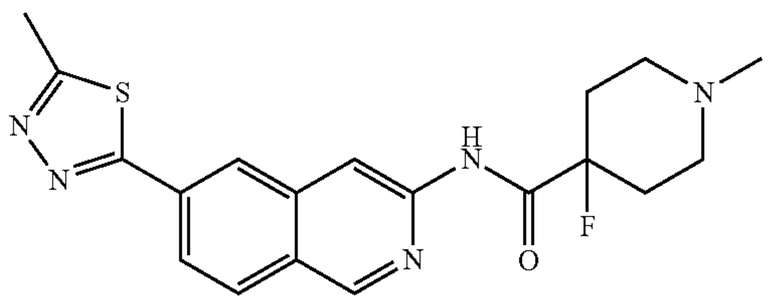
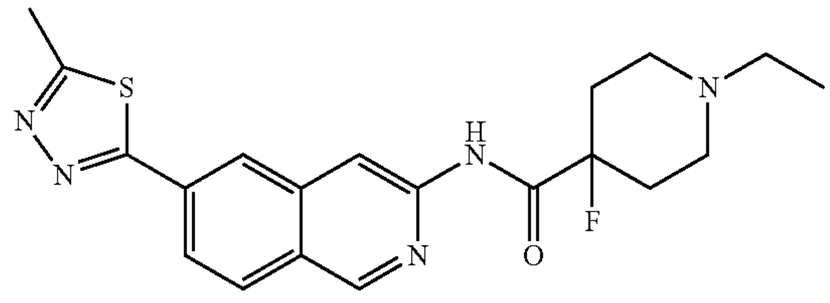
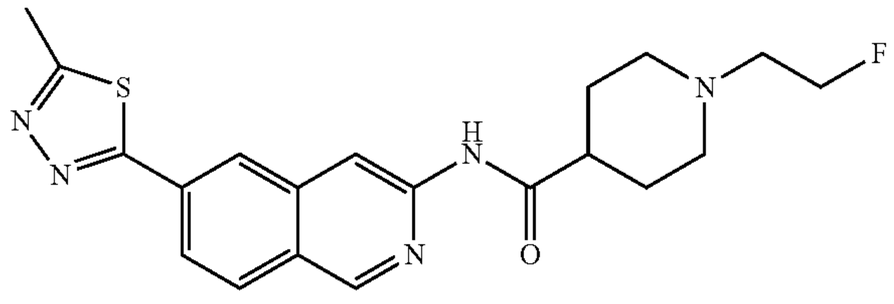
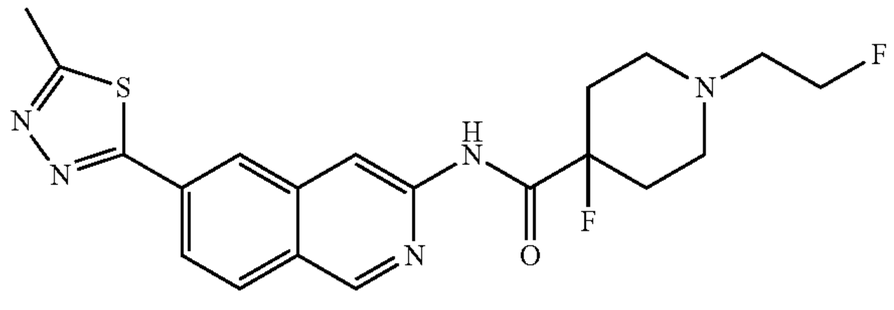
	894
	895
	896
	897
	898
	899
	900
	901

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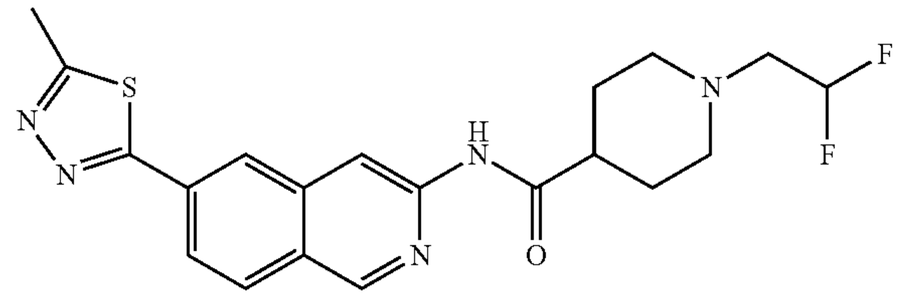

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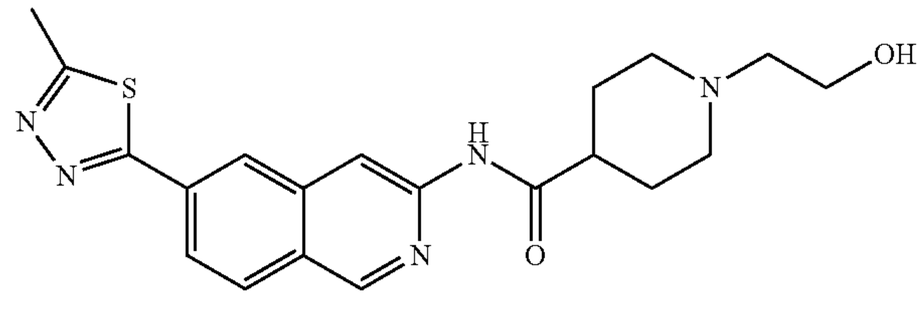

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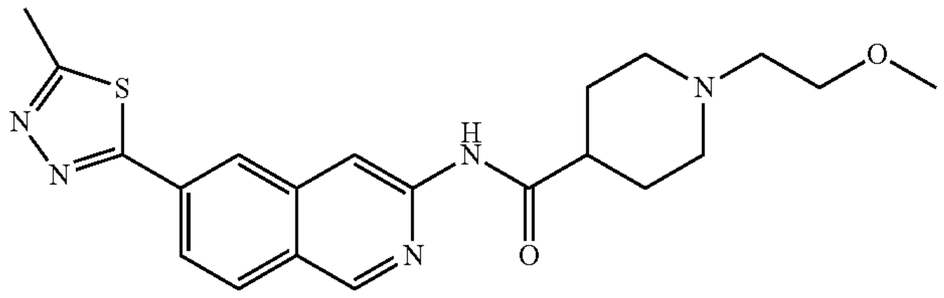

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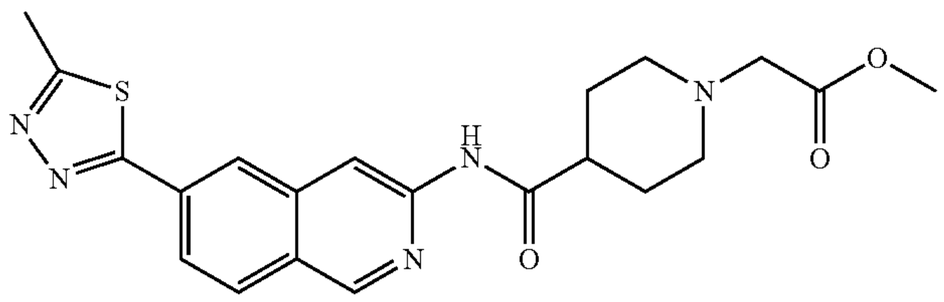

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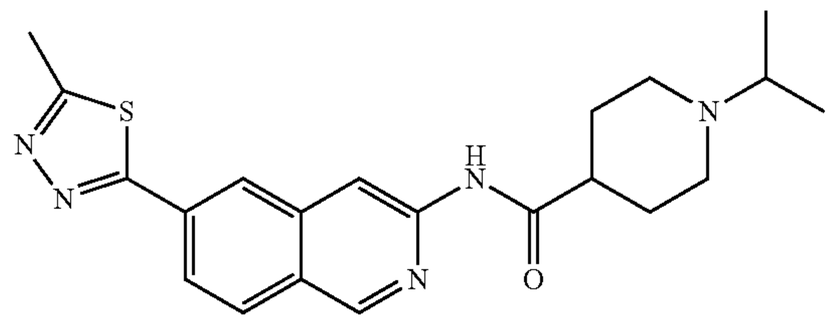

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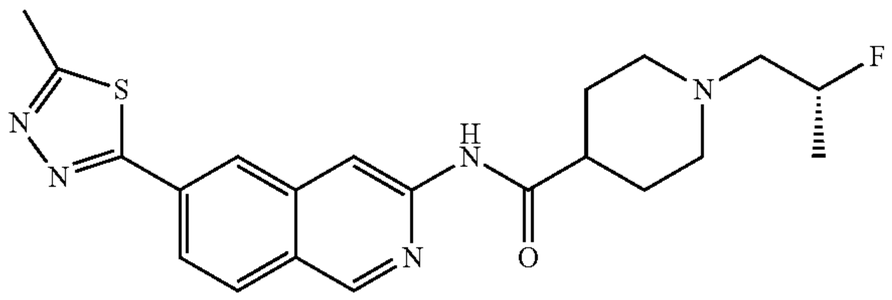

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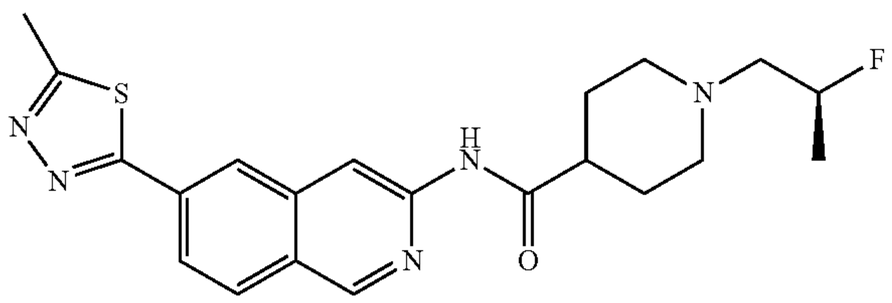

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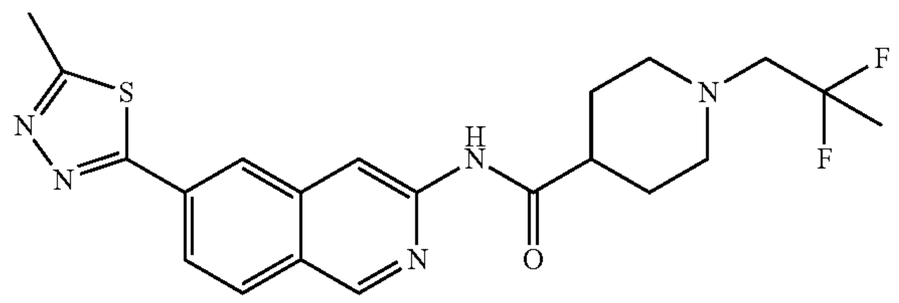

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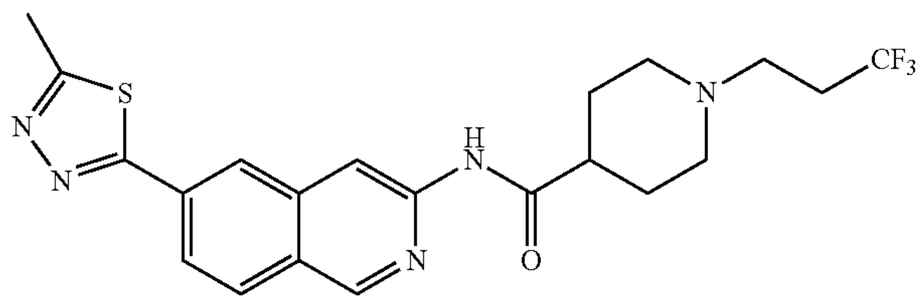

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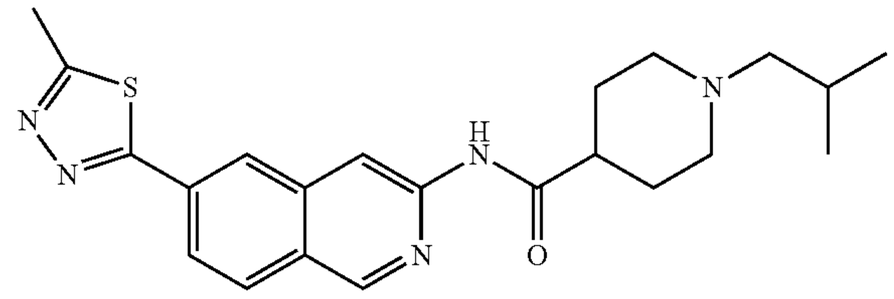

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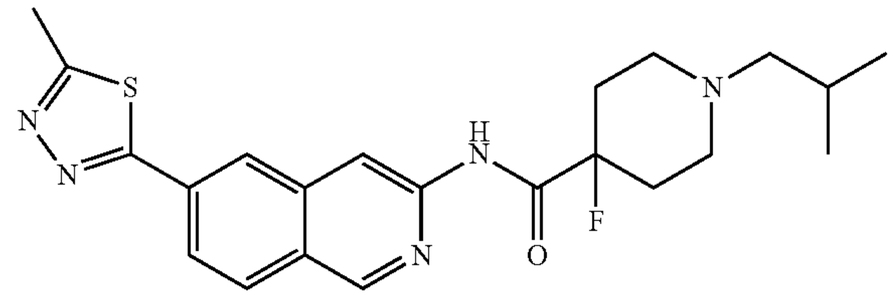

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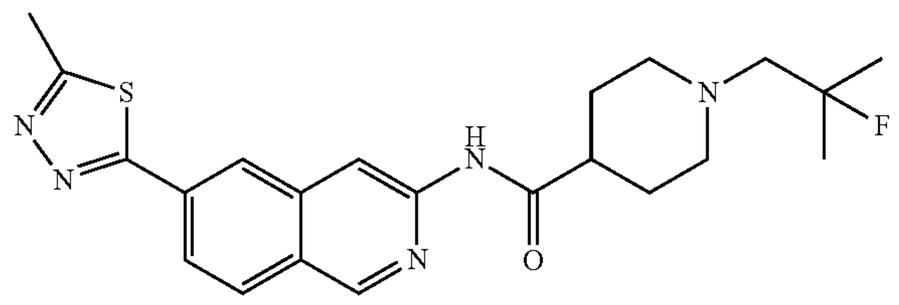

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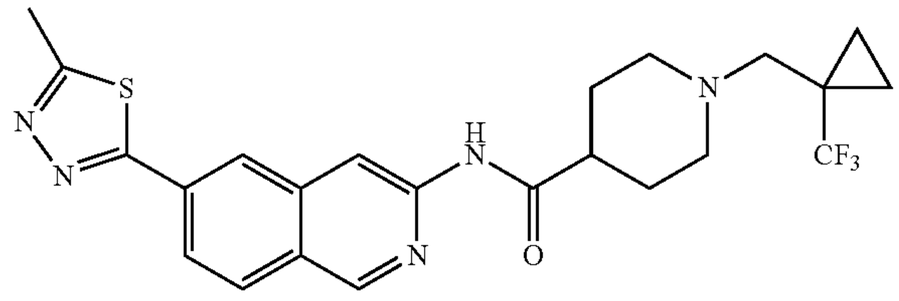

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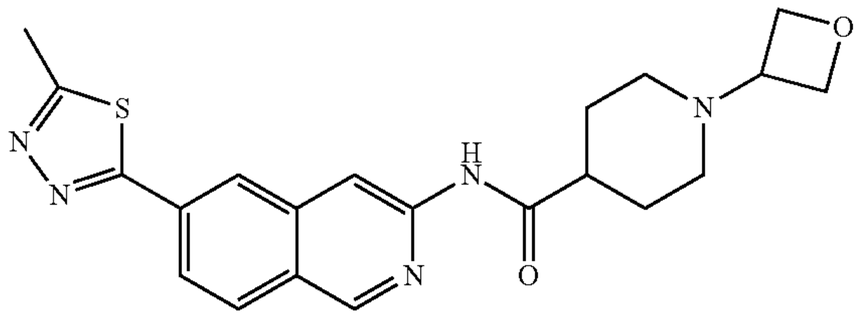

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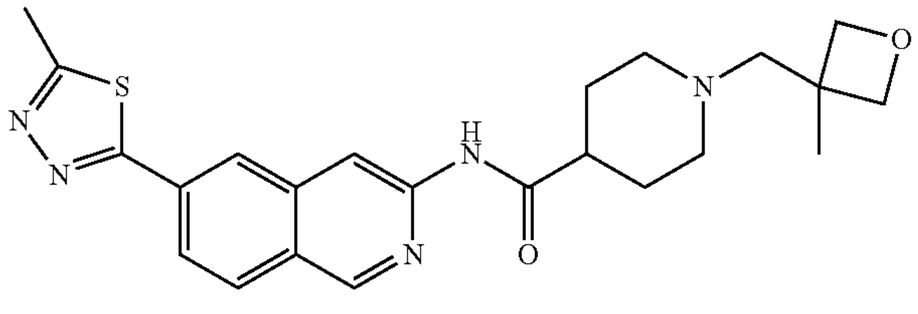

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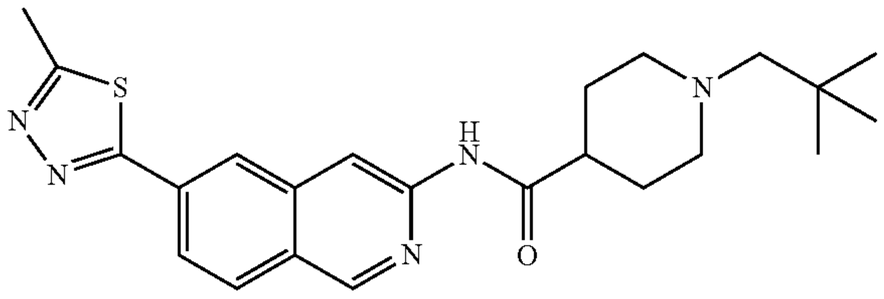
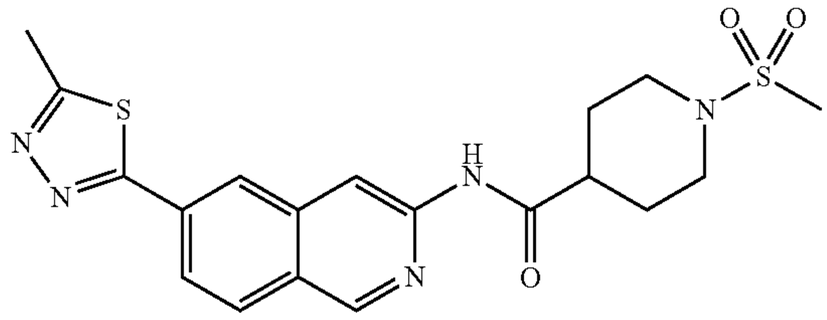
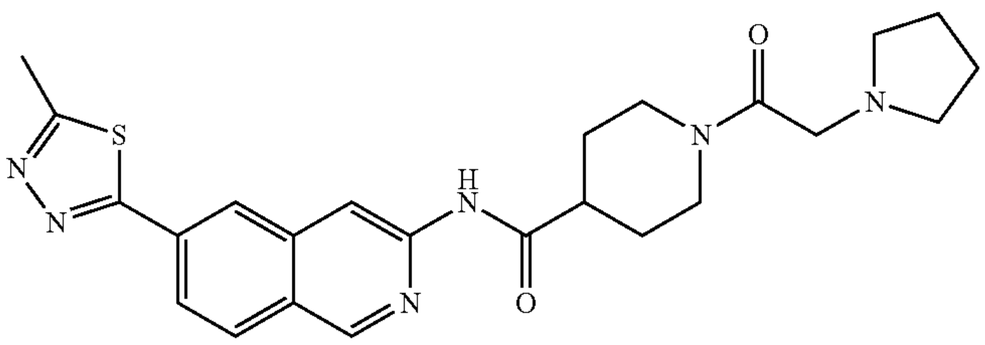
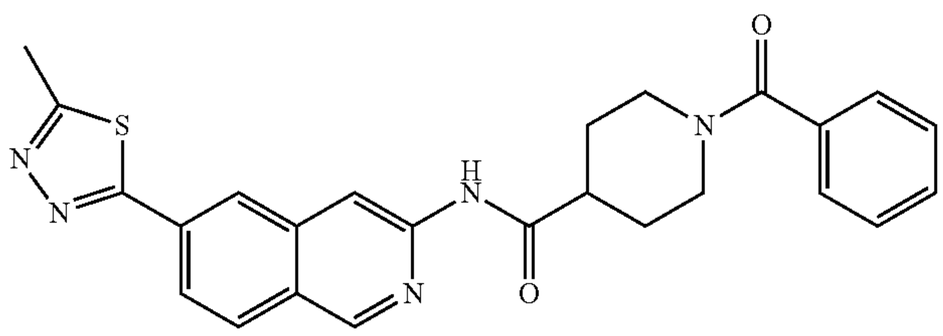
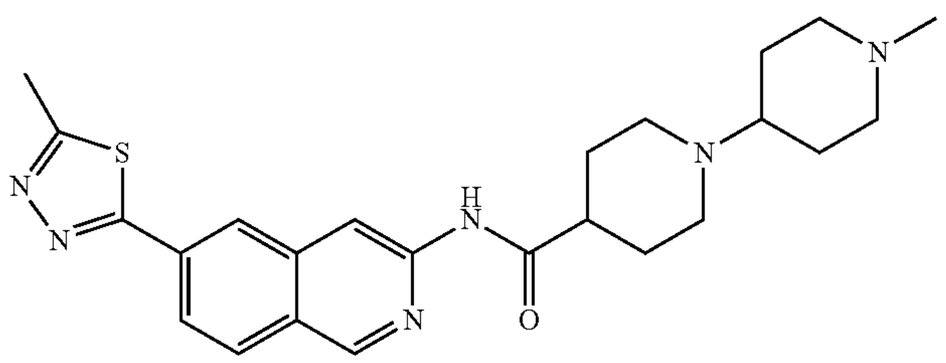
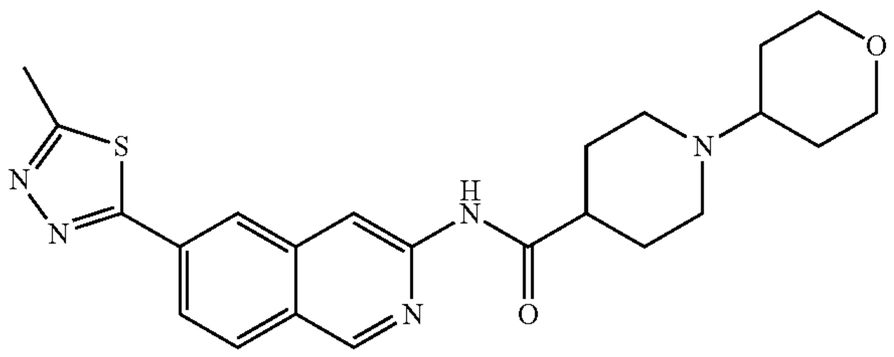
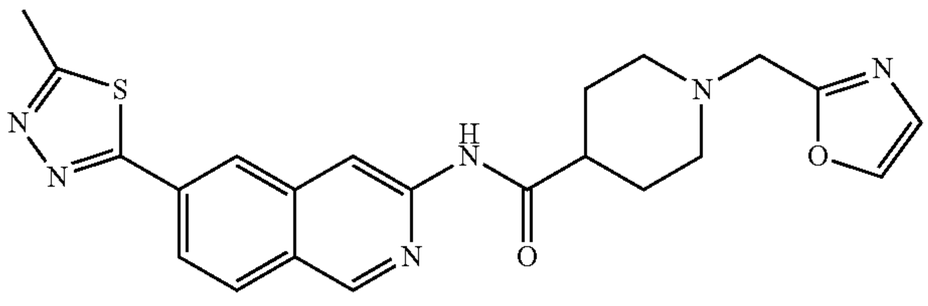
918	
919	
920	
921	
922	
923	
924	

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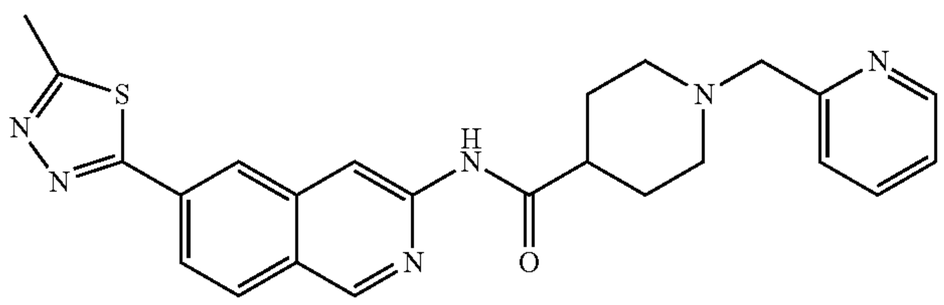

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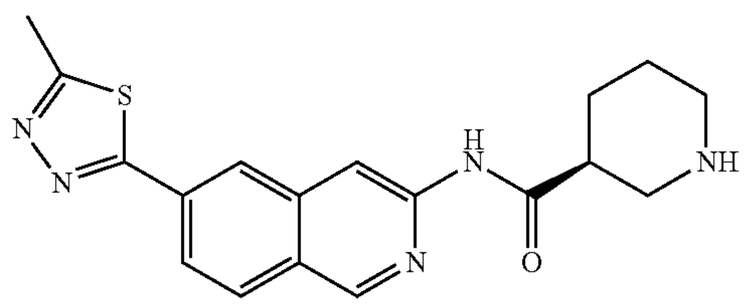

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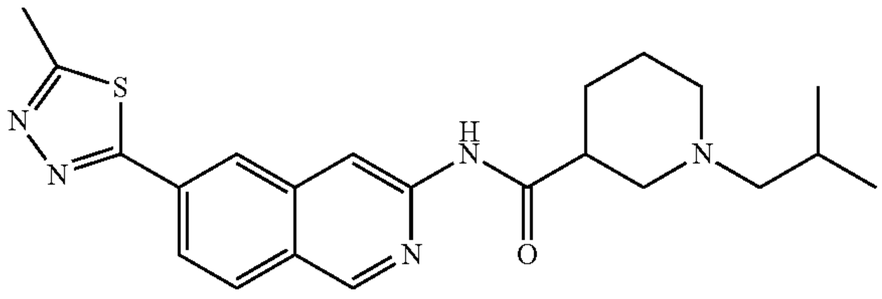

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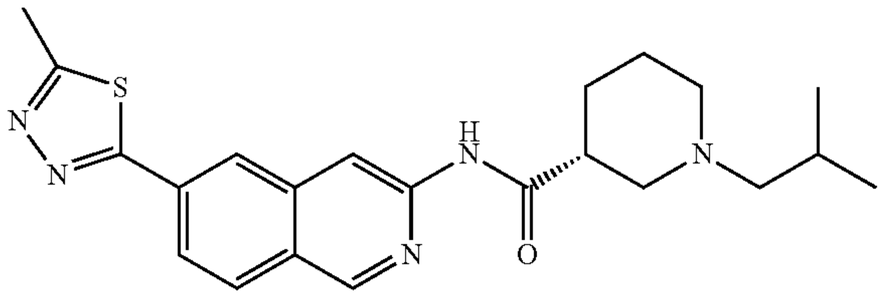

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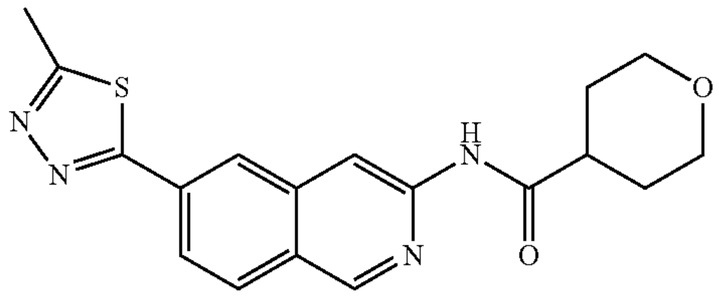

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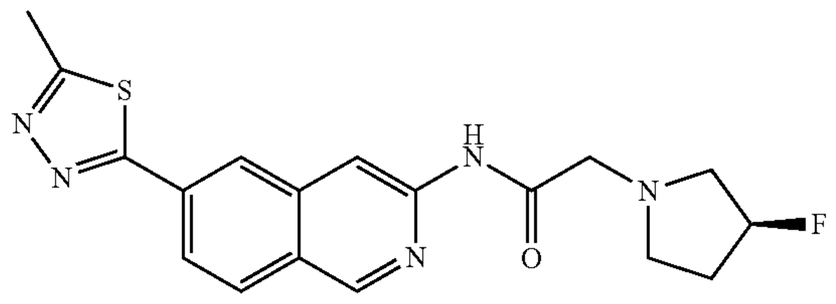
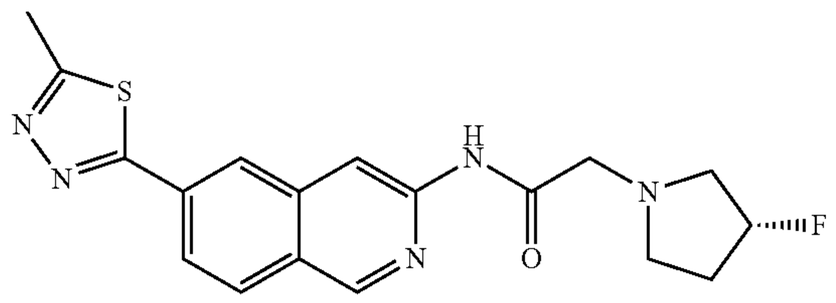
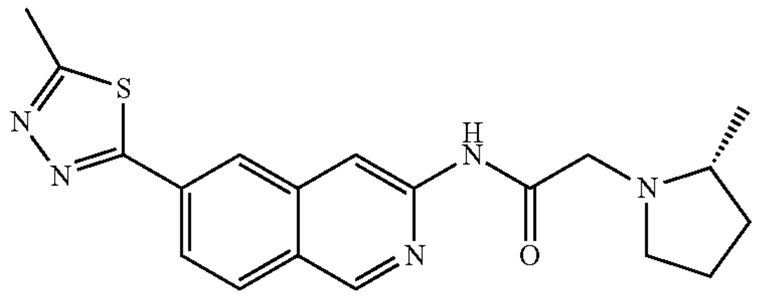
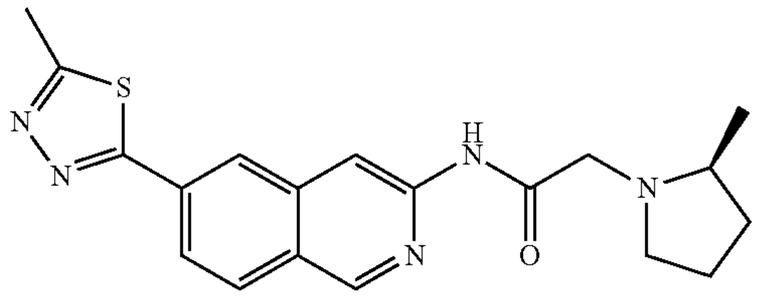
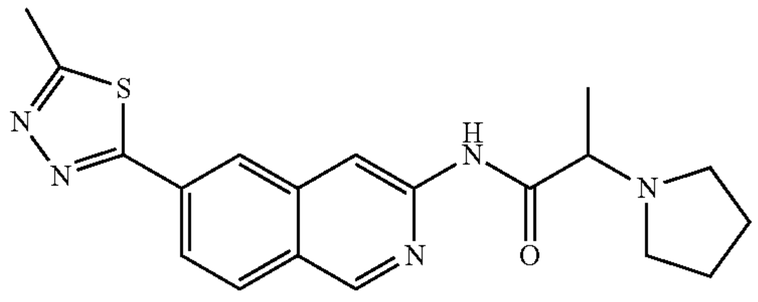
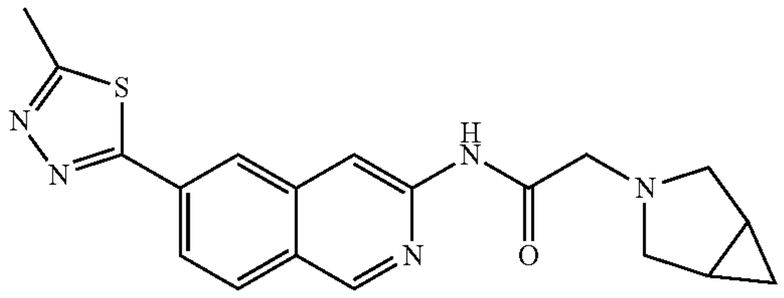
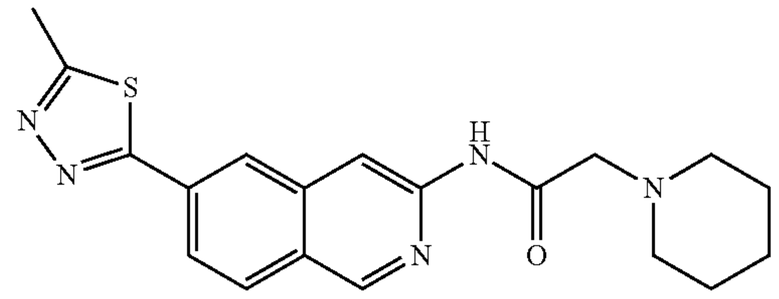
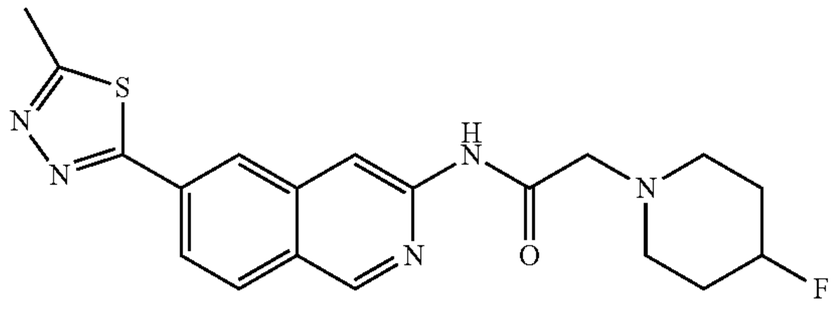
933	
934	
935	
936	
937	
938	
939	
940	

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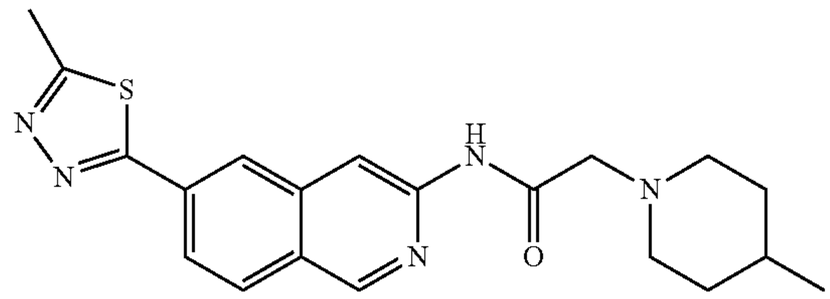

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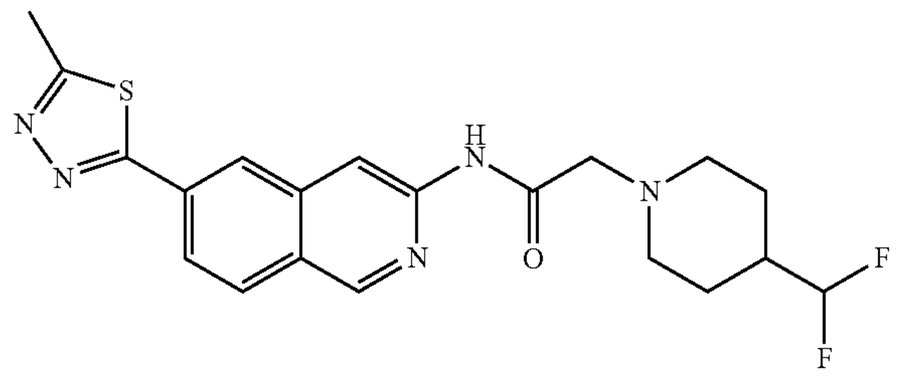

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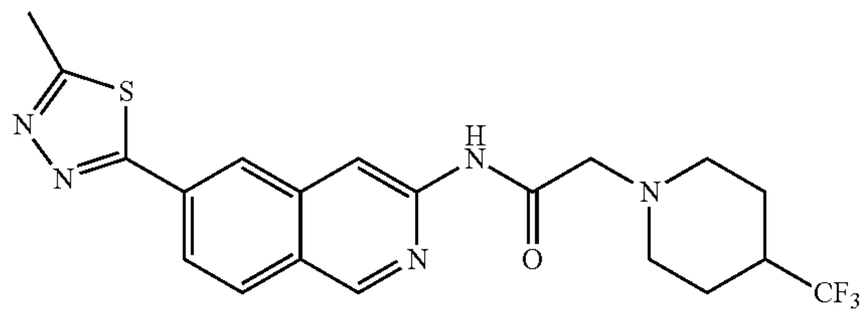

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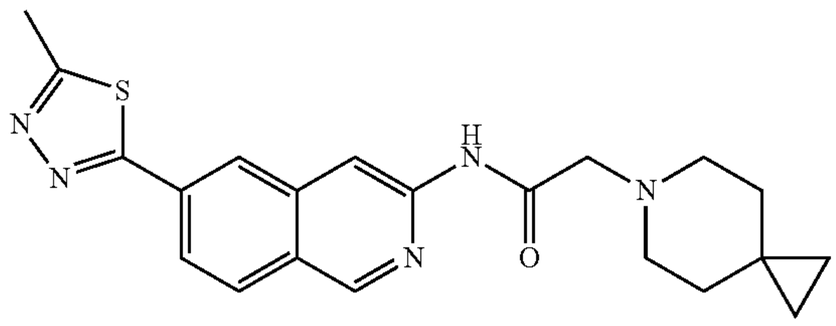

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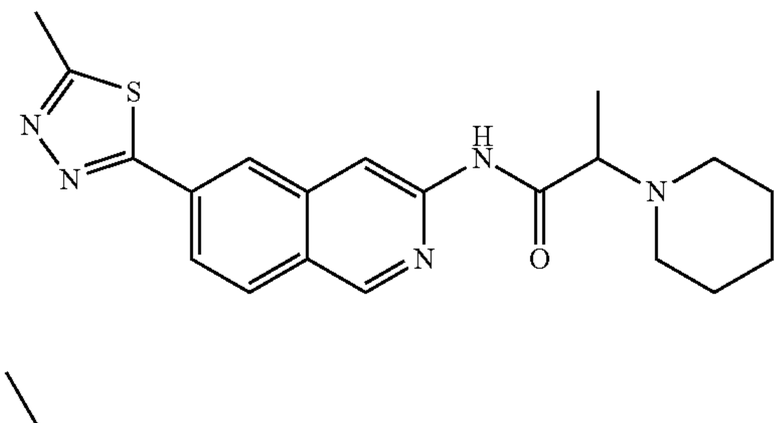

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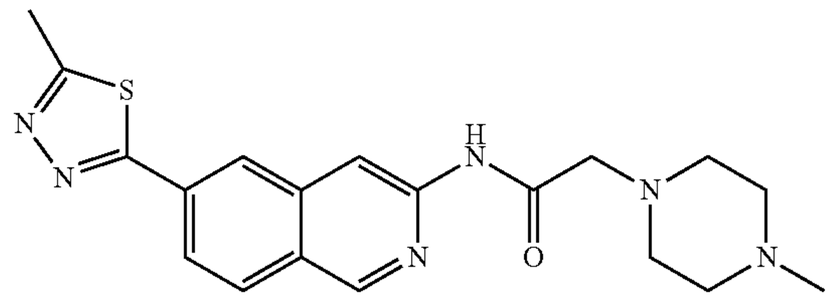

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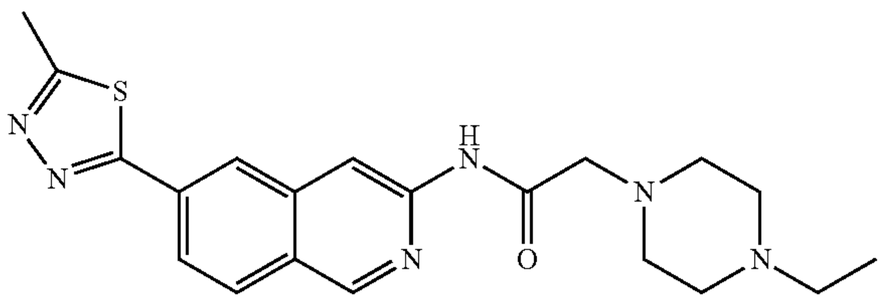

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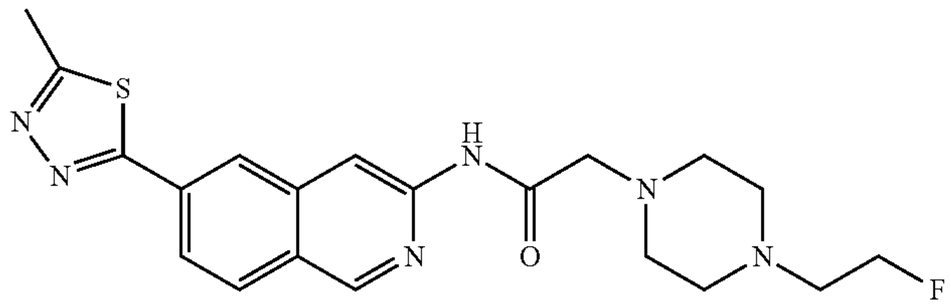

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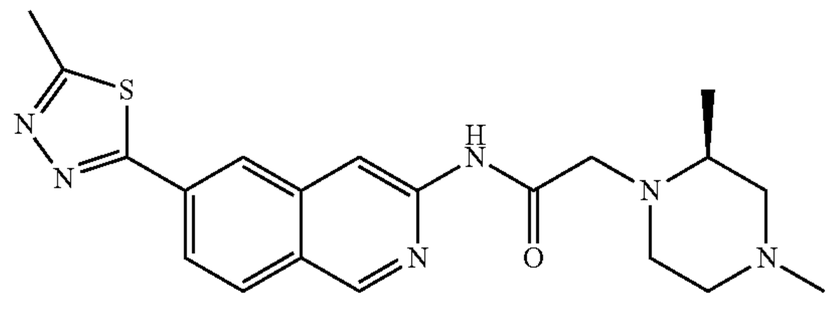

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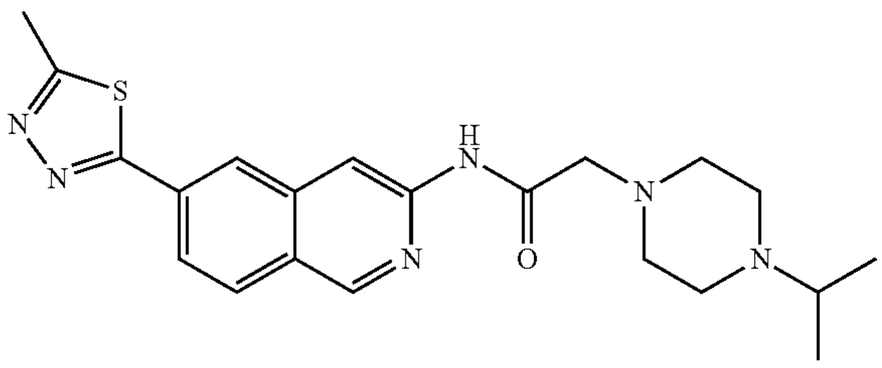

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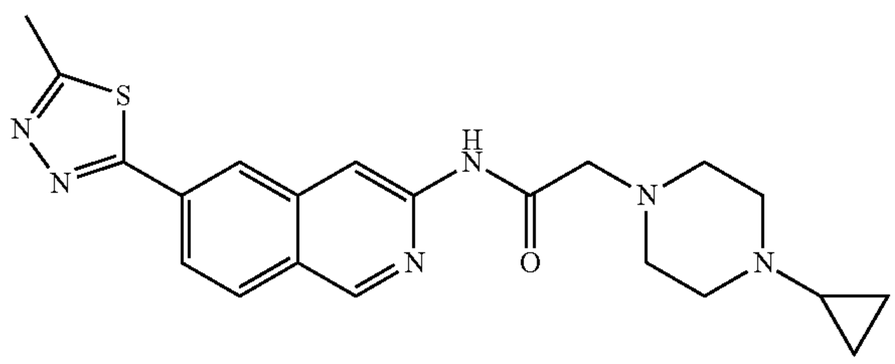

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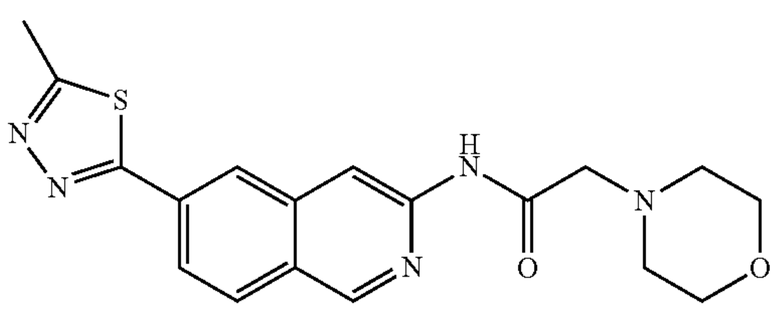

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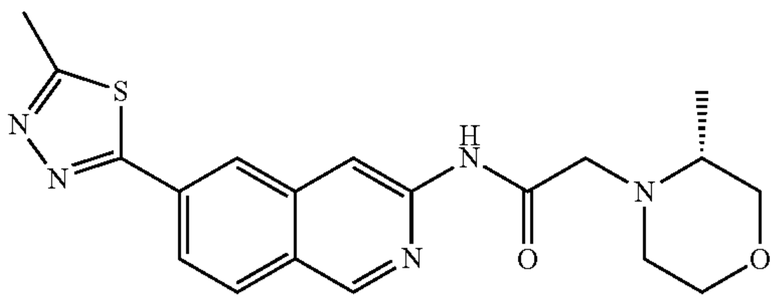

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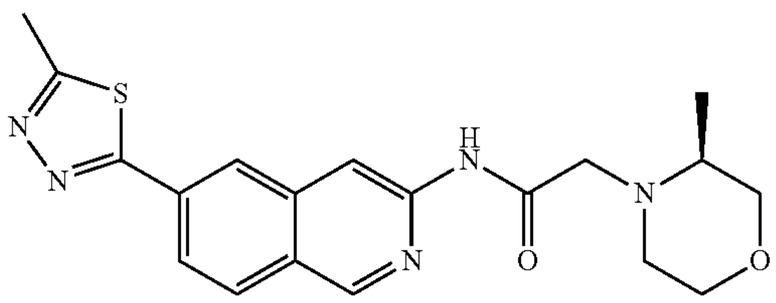

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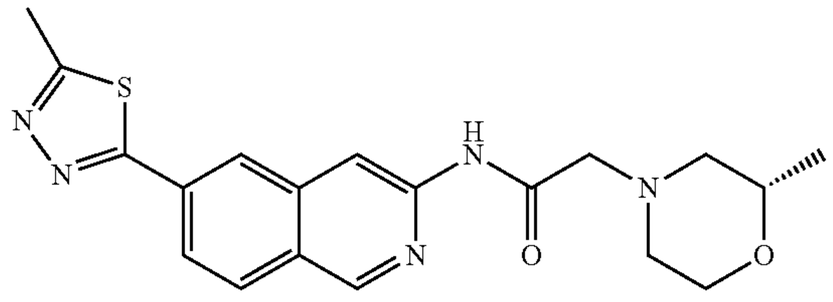
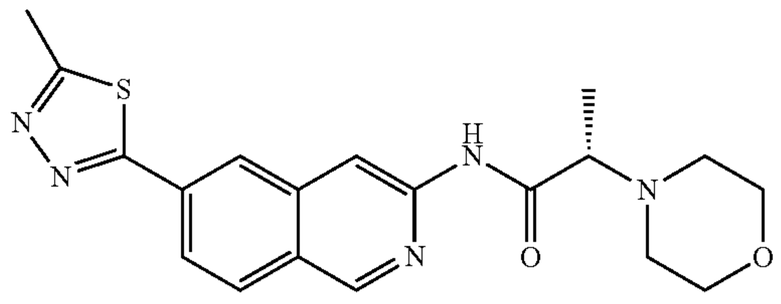
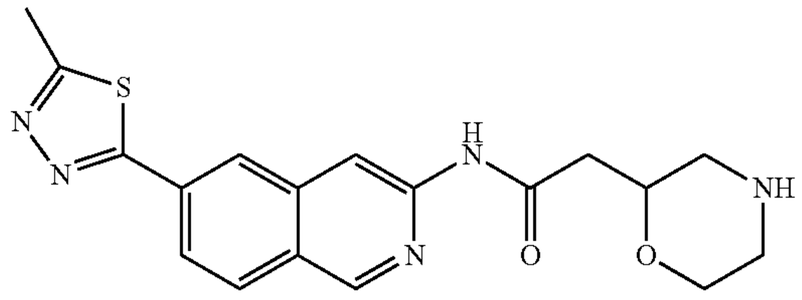
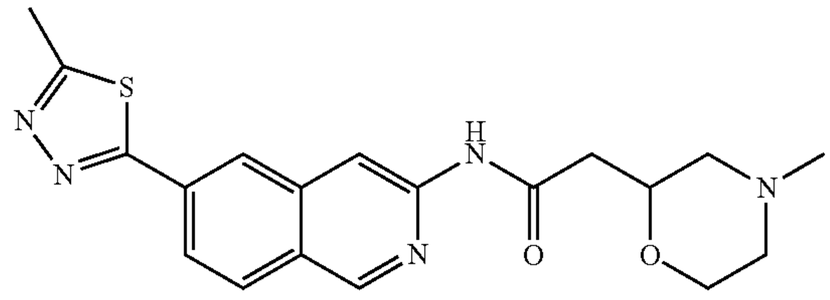
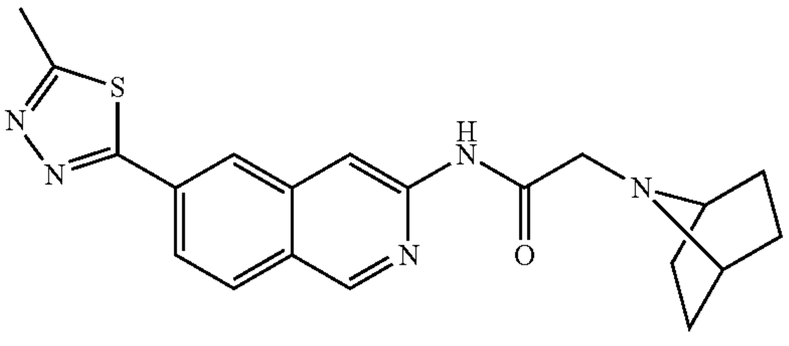
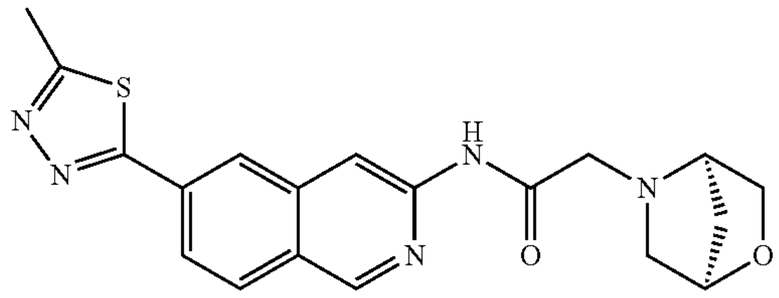
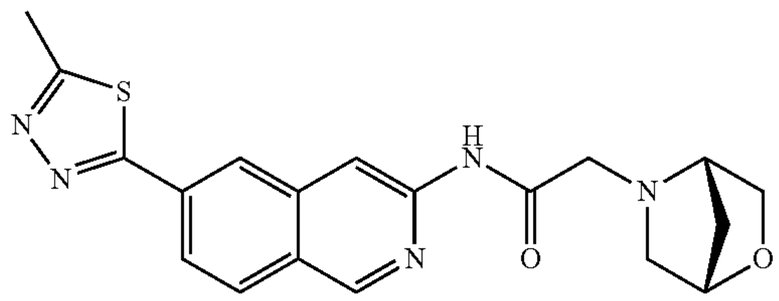
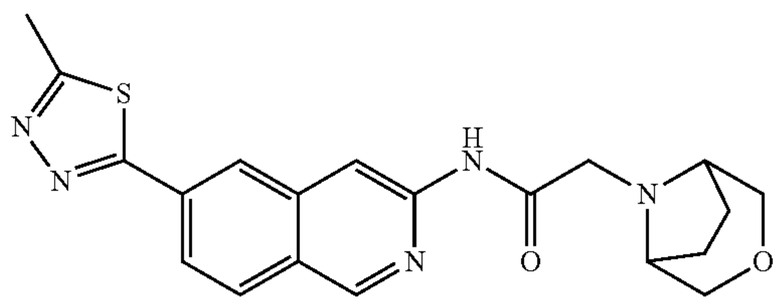
	955
	956
	957
	958
	959
	960
	961
	962

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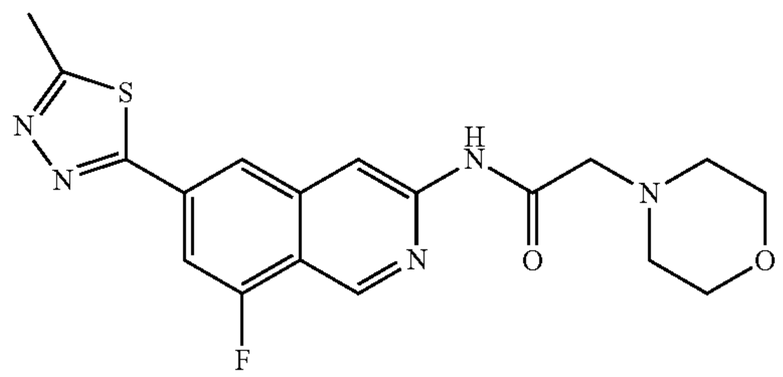	
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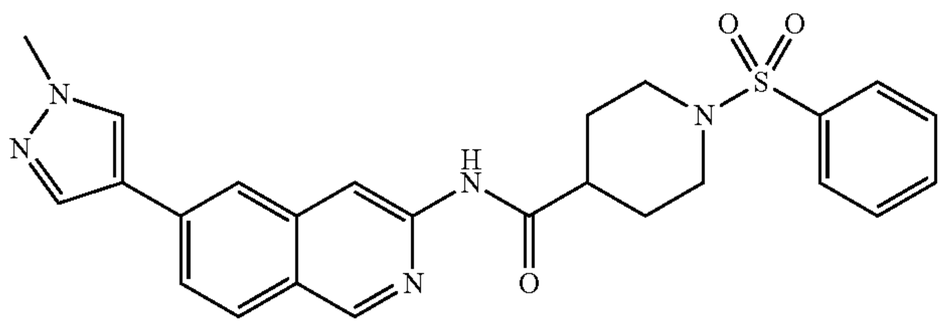	
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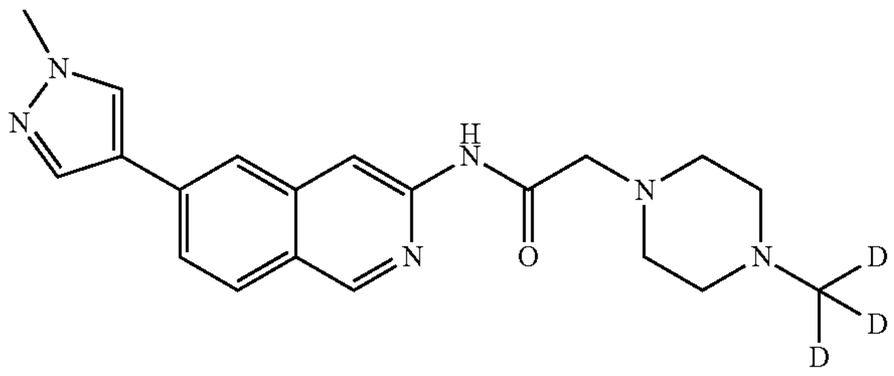	
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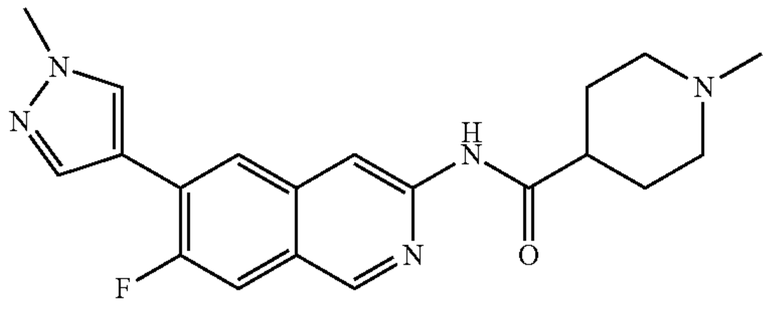	
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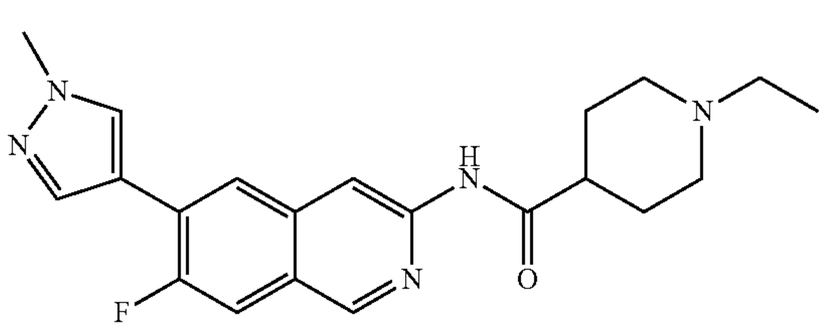	
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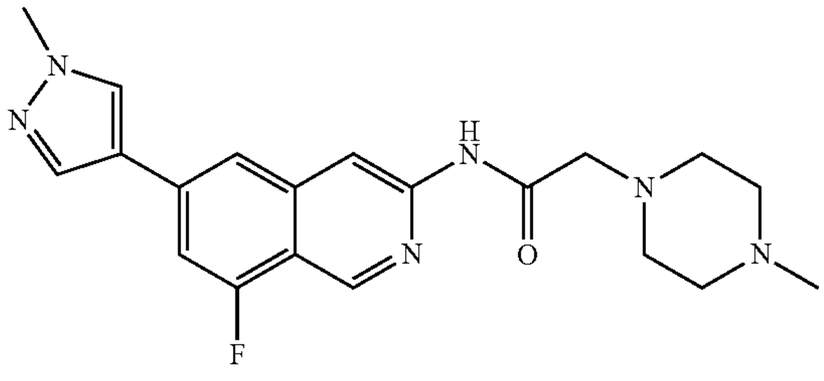	

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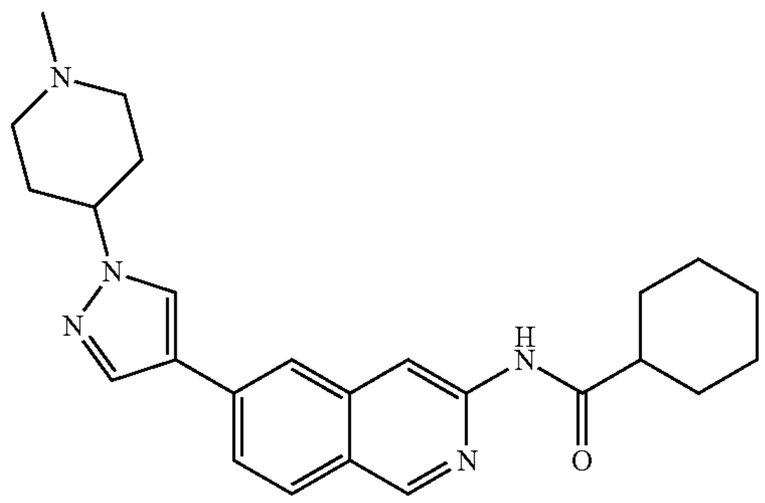
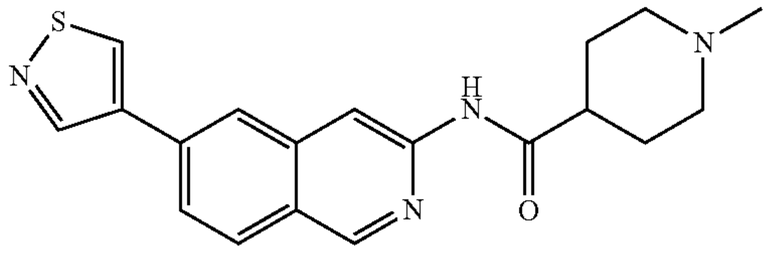
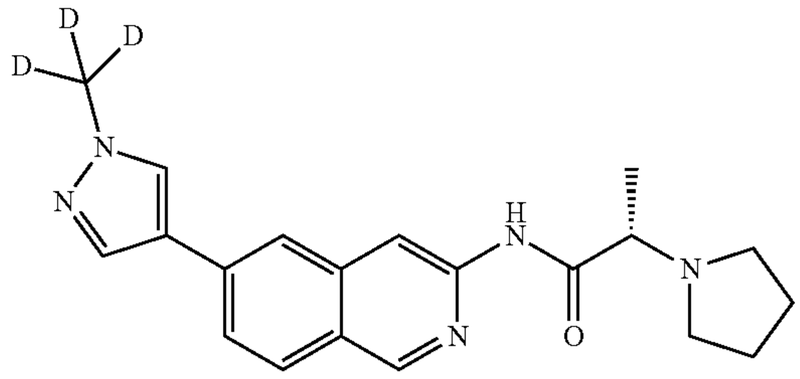
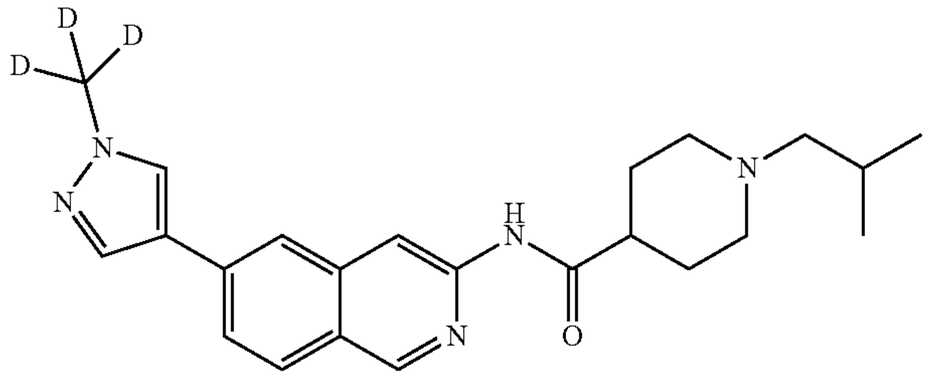
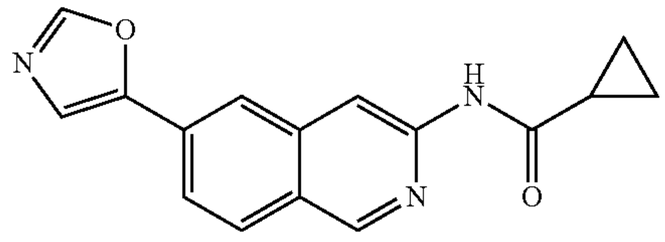
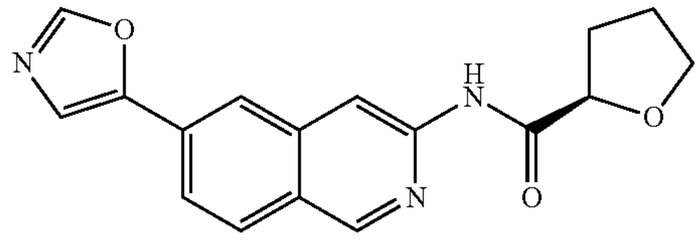
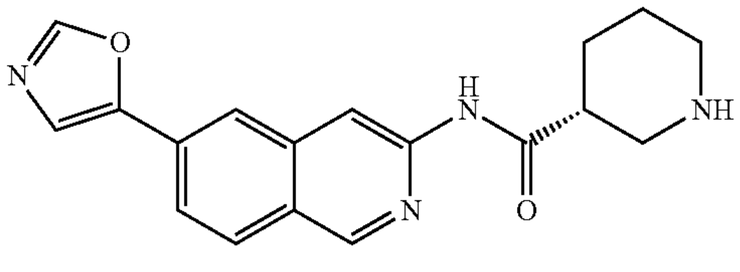
969	
970	
971	
972	
973	
974	
975	

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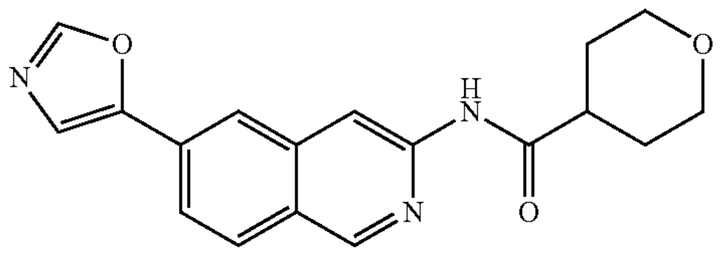
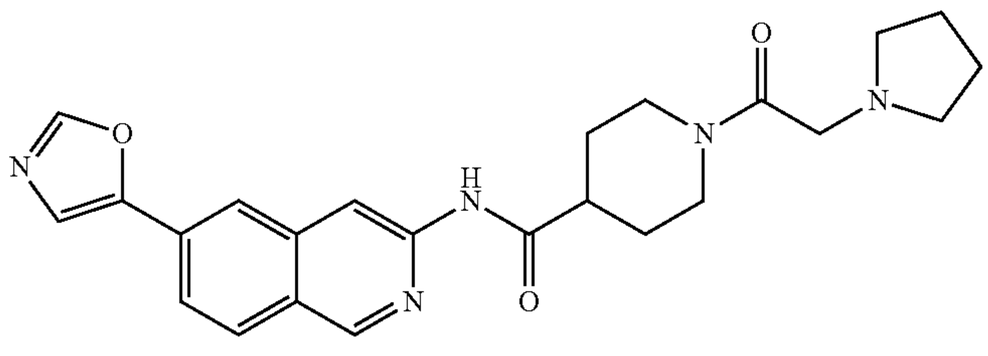
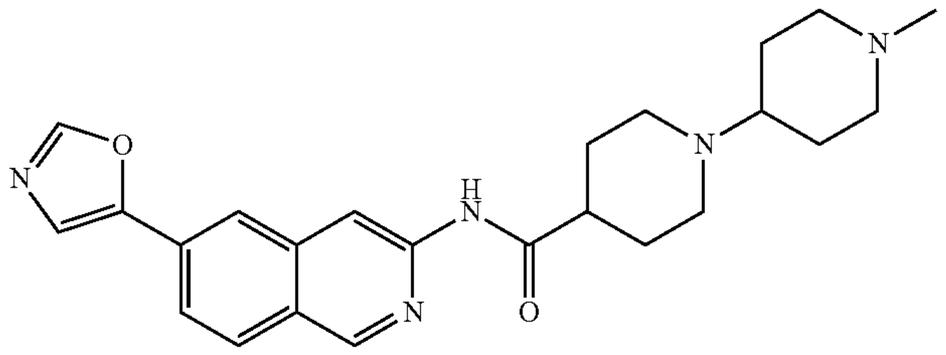
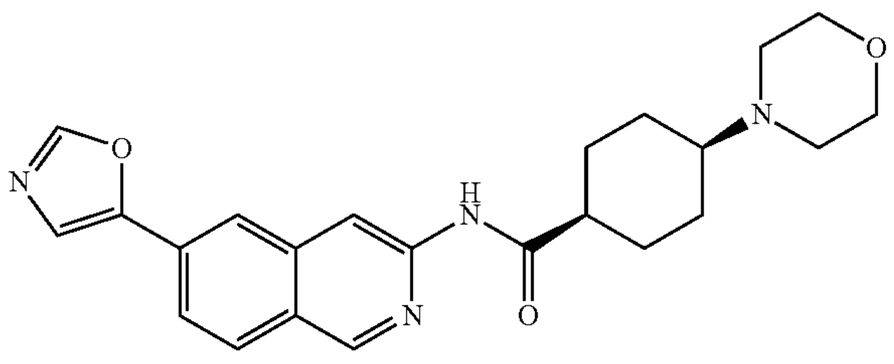
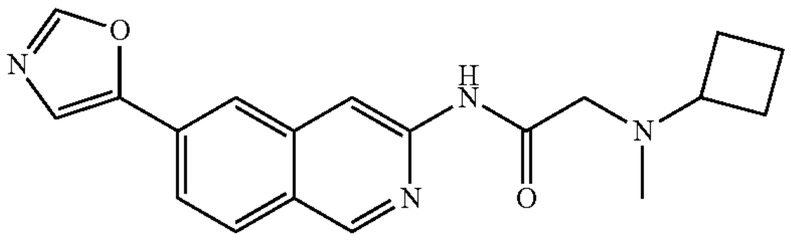
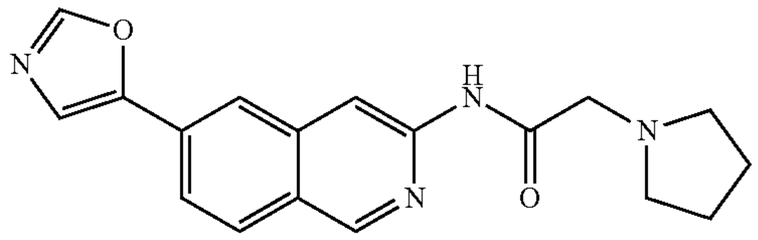
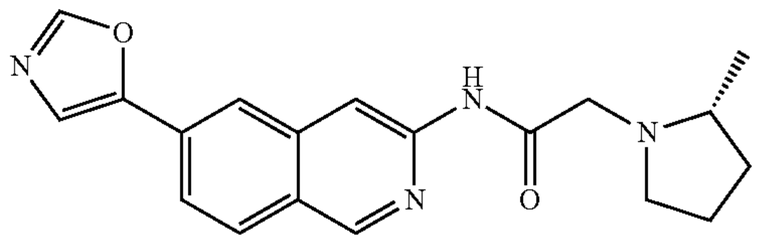
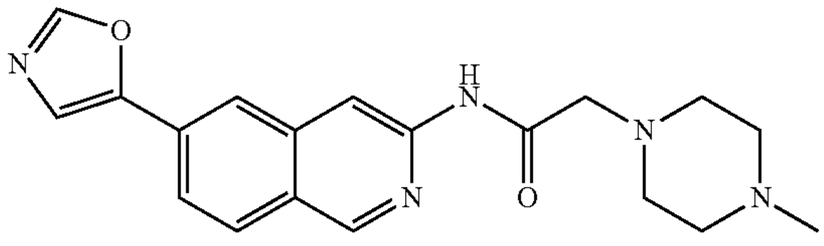
	976
	977
	978
	979
	980
	981
	982
	983

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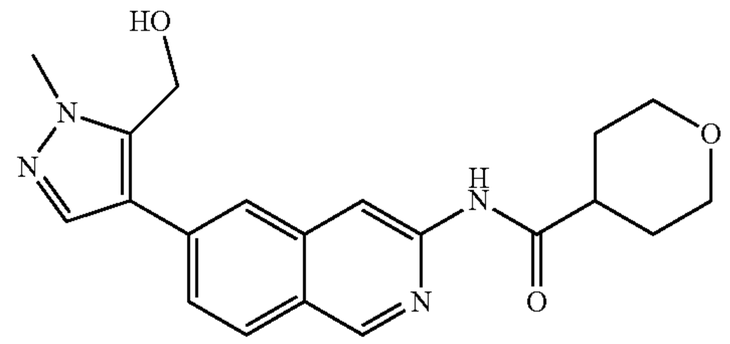
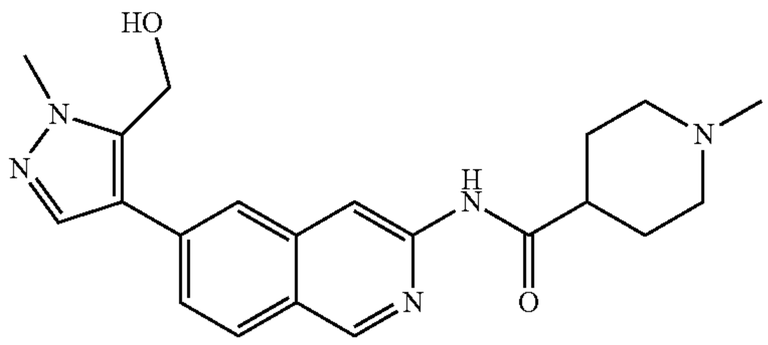
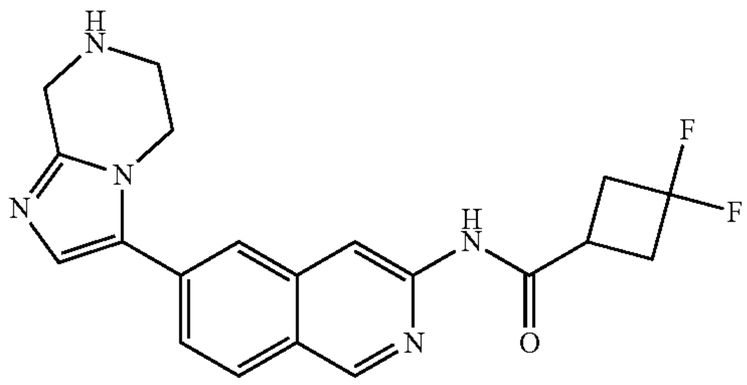
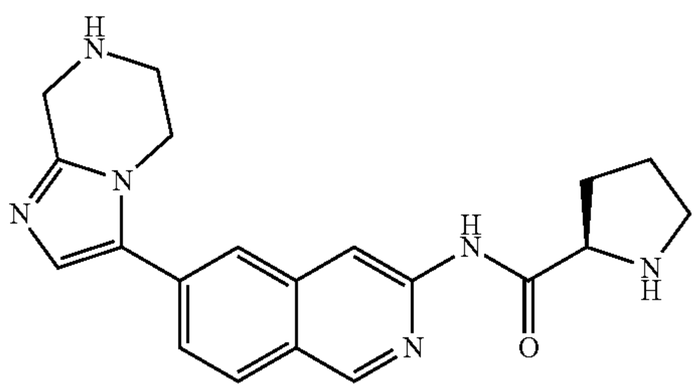
	984
	985
	986
	987
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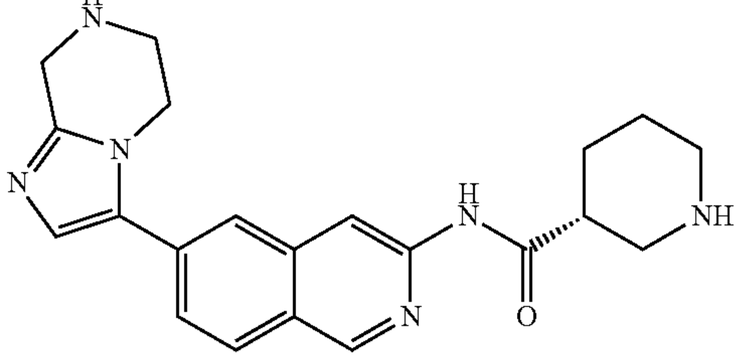	
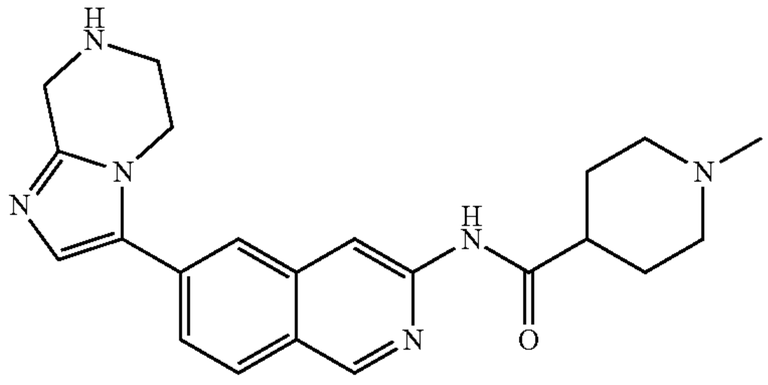	989

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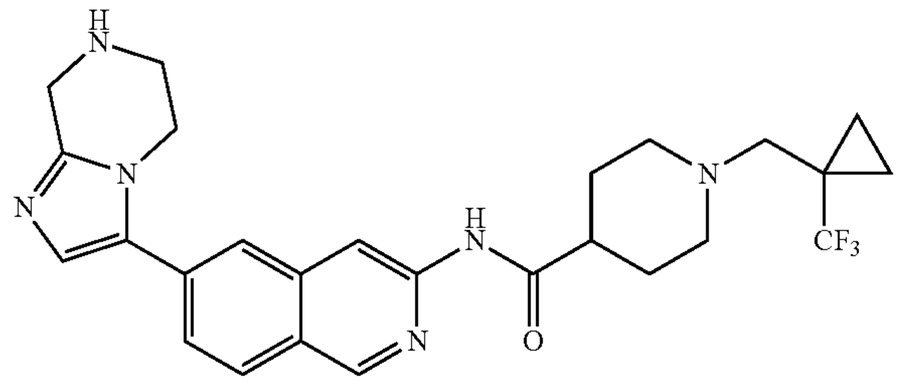

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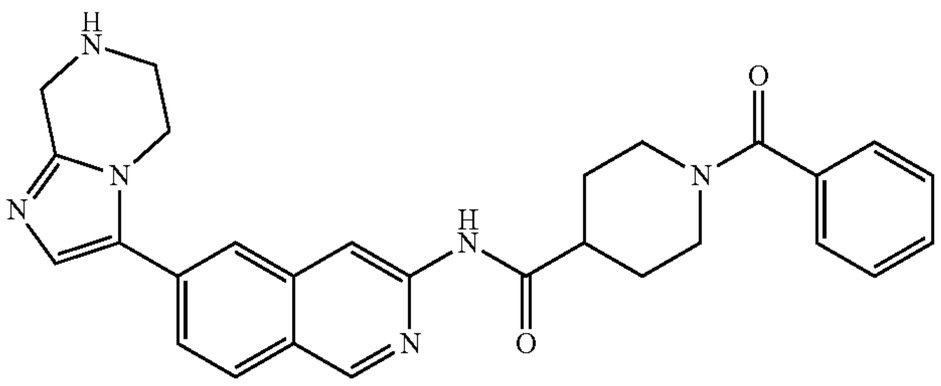

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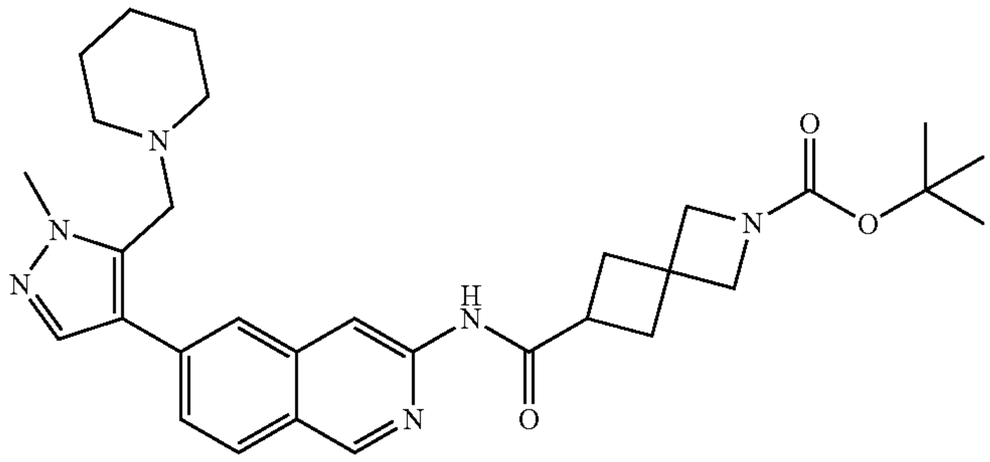

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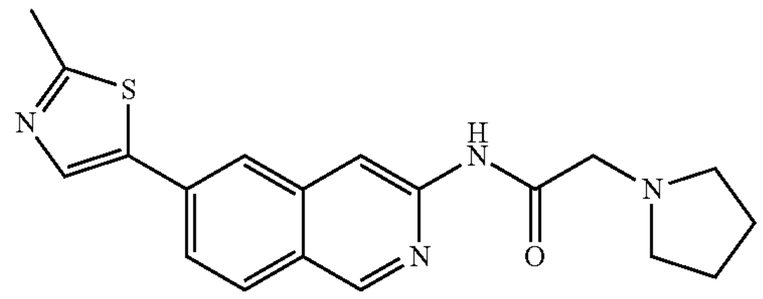

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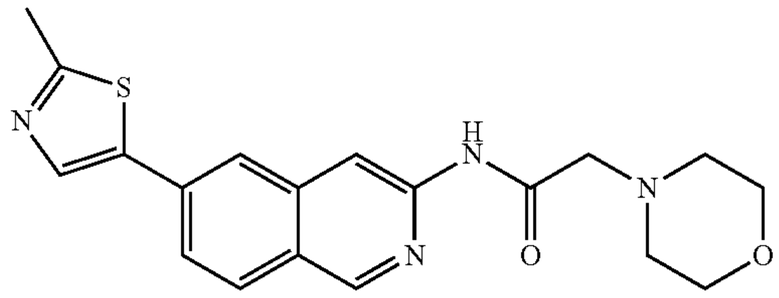

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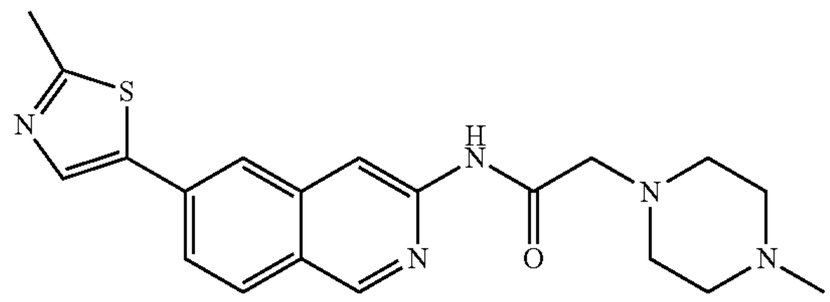

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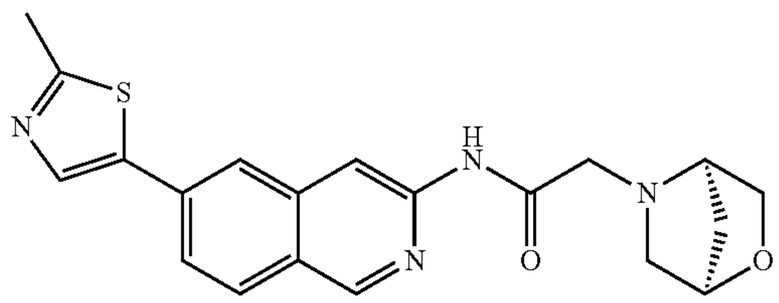

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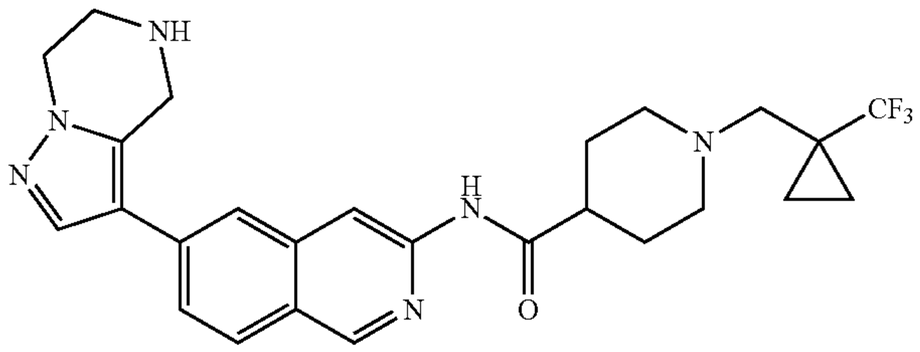

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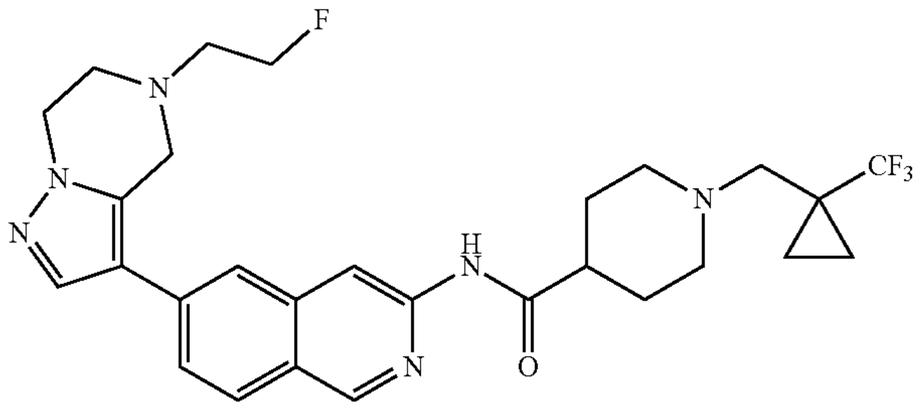

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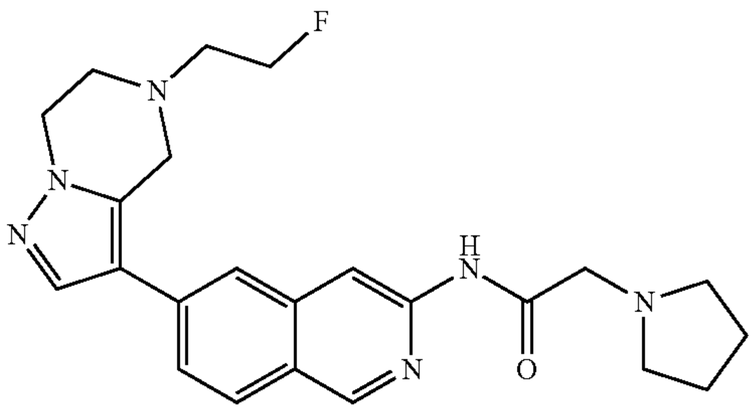

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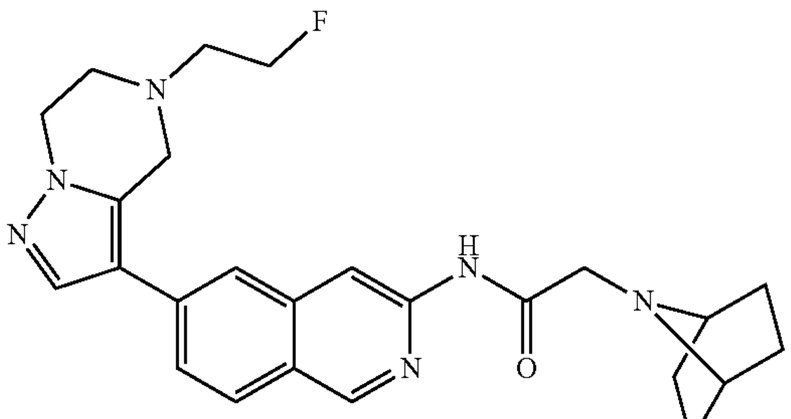

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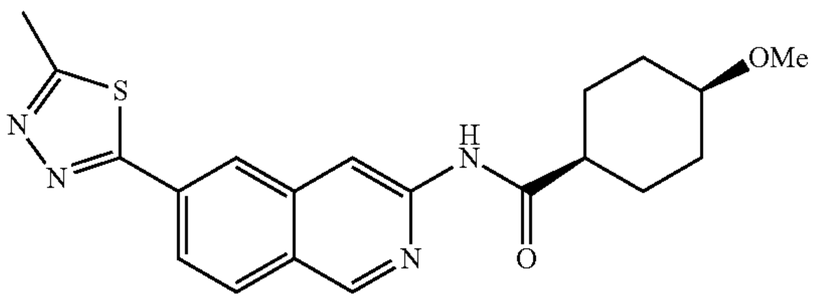

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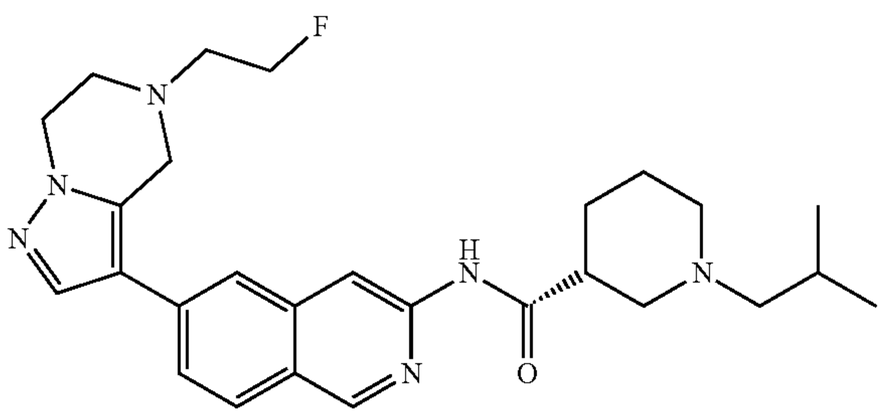

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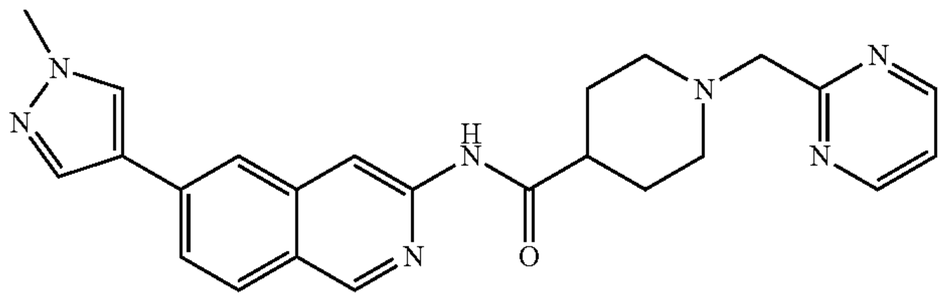
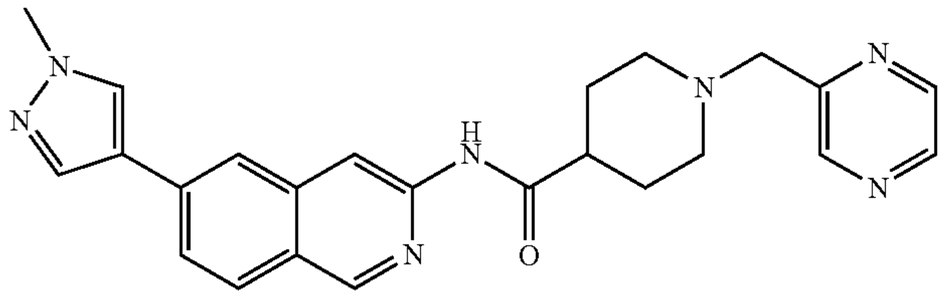
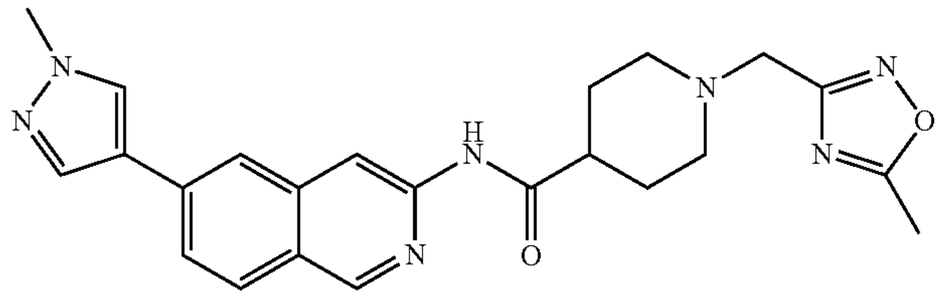
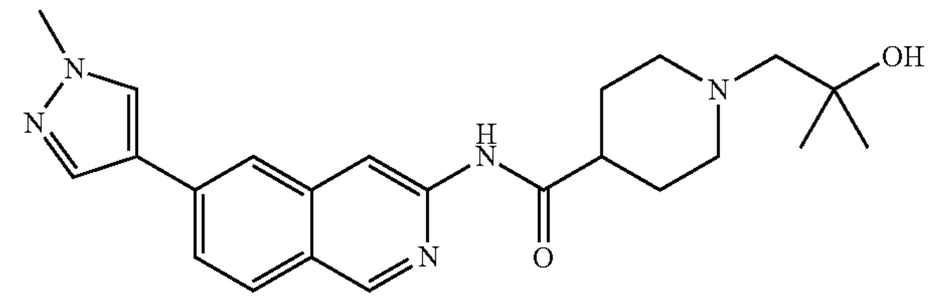
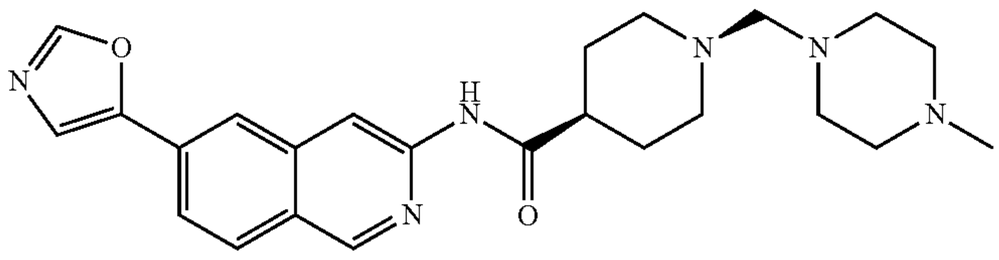
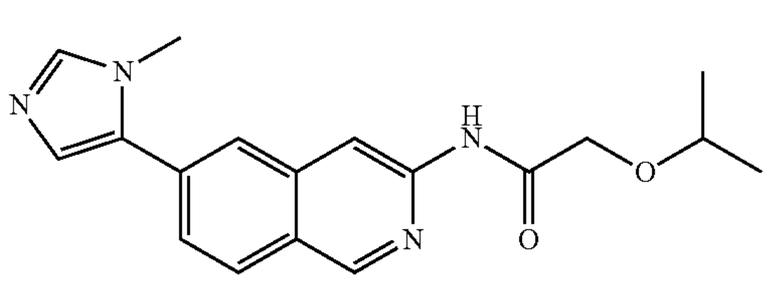
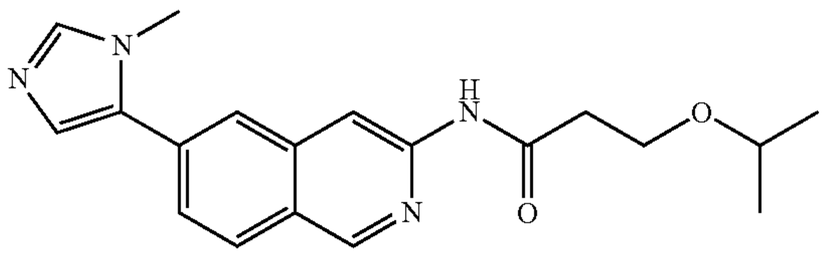
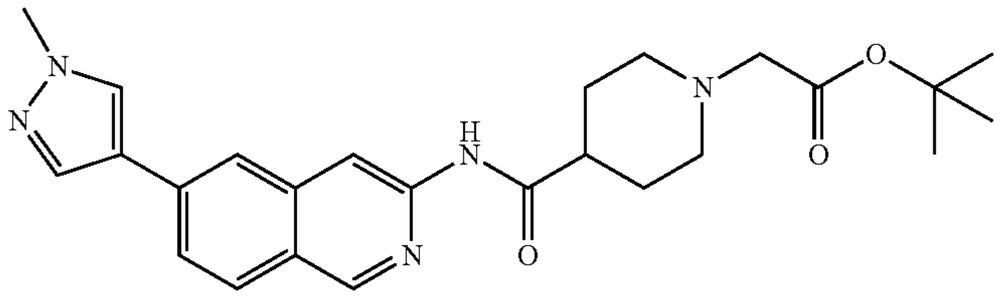
	1003
	1004
	1005
	1006
	1007
	1008
	1009
	1010

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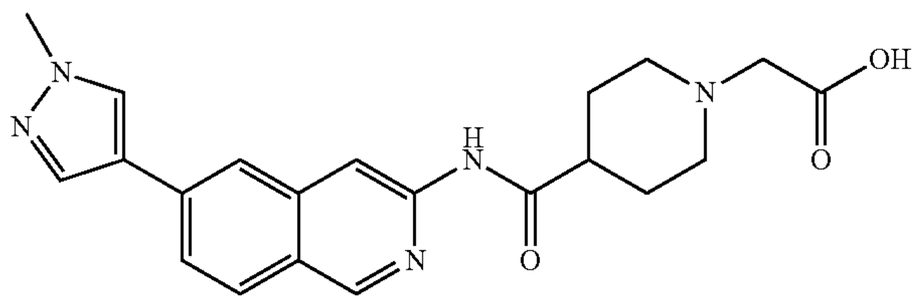
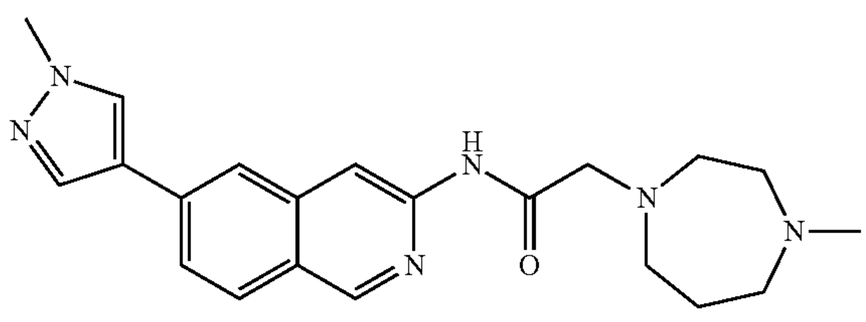
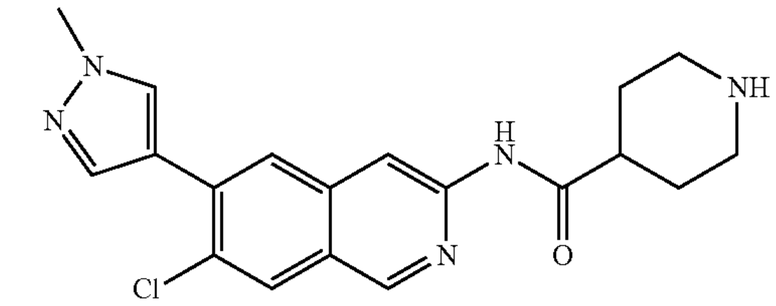
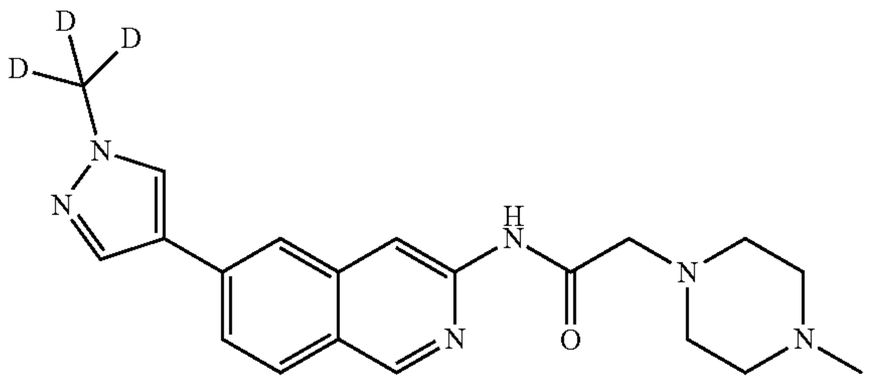
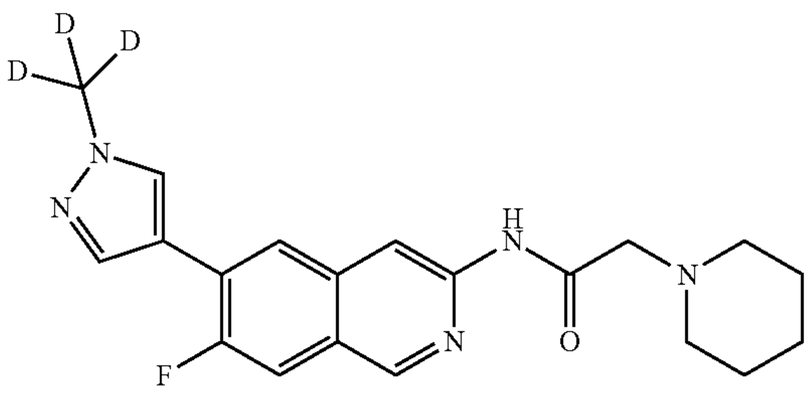
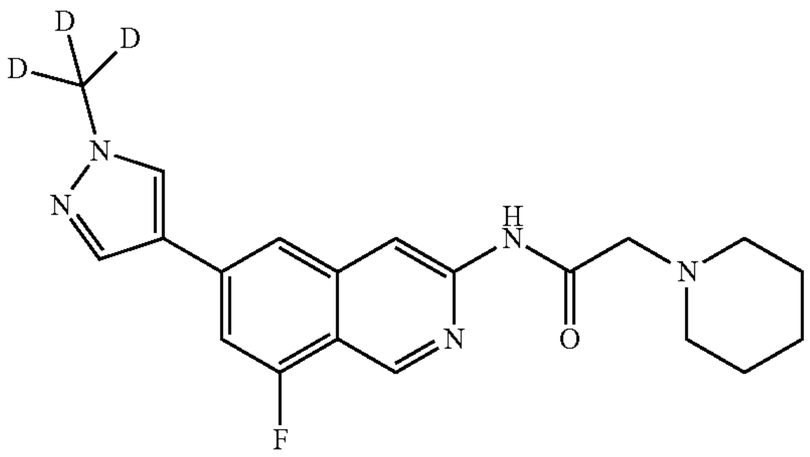
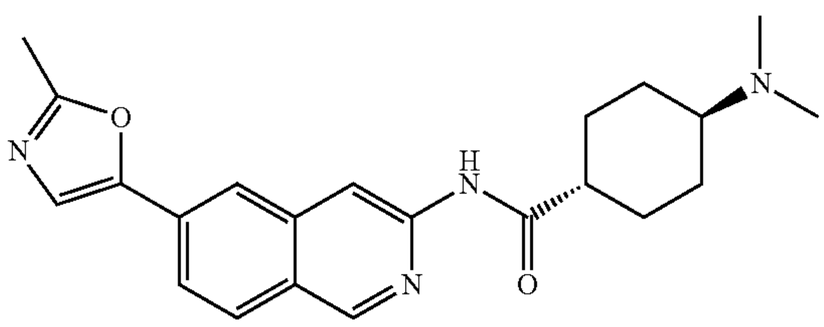
	1011
	1012
	1013
	1014
	1015
	1016
	1017

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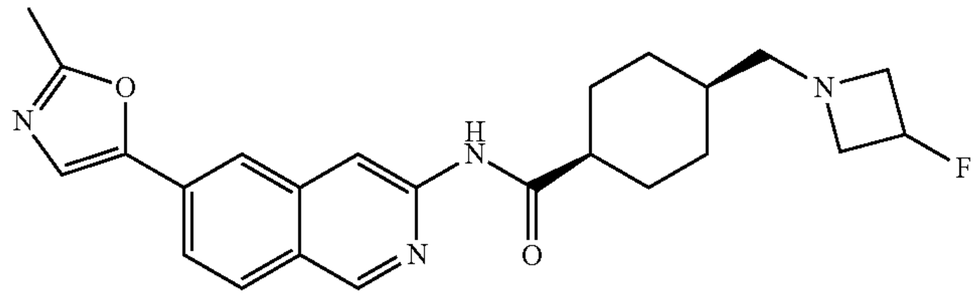
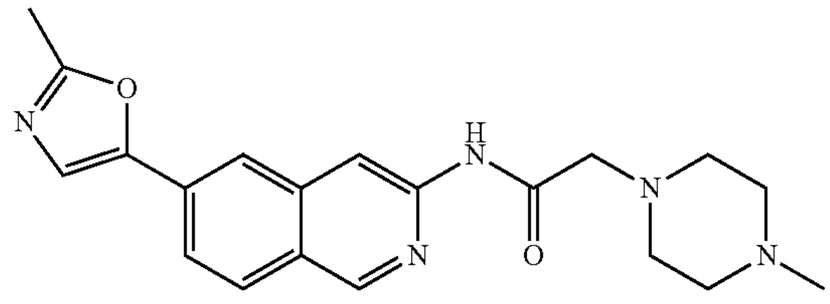
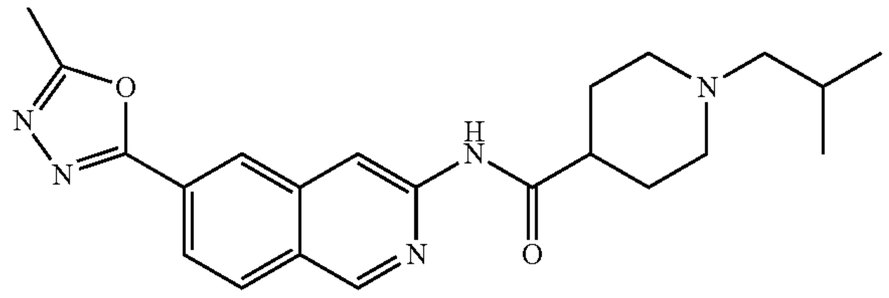
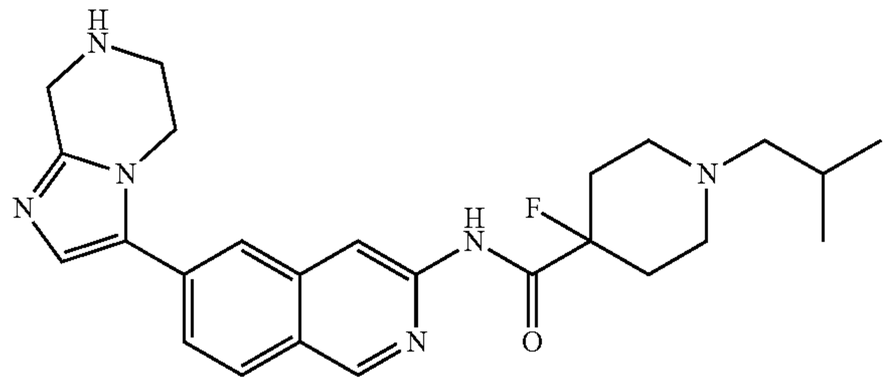
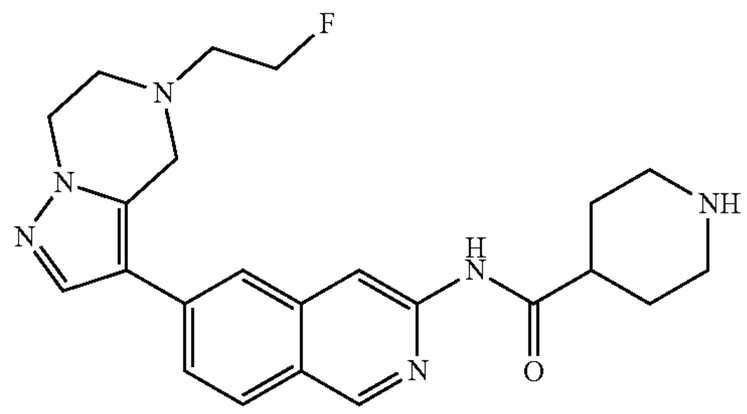
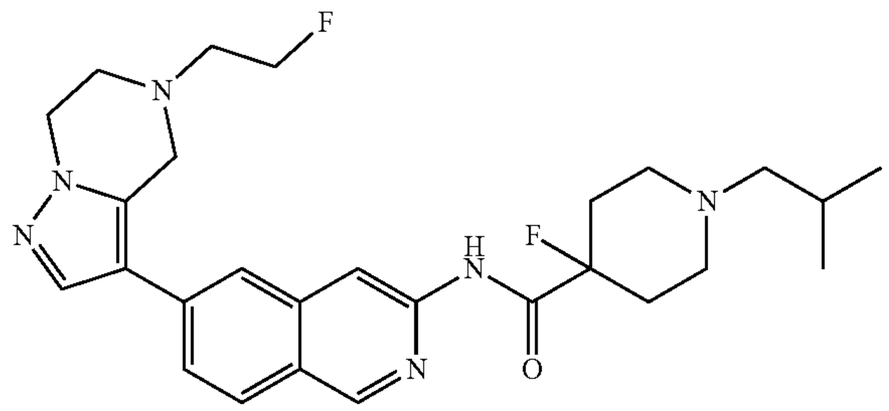
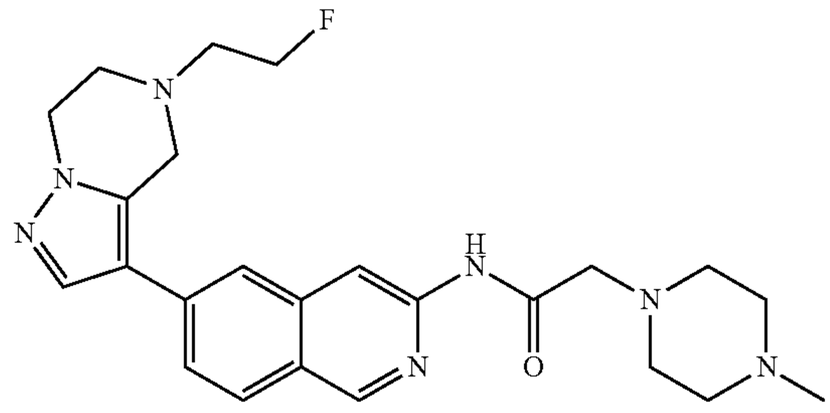
1018	
1019	
1020	
1021	
1022	
1023	
1024	

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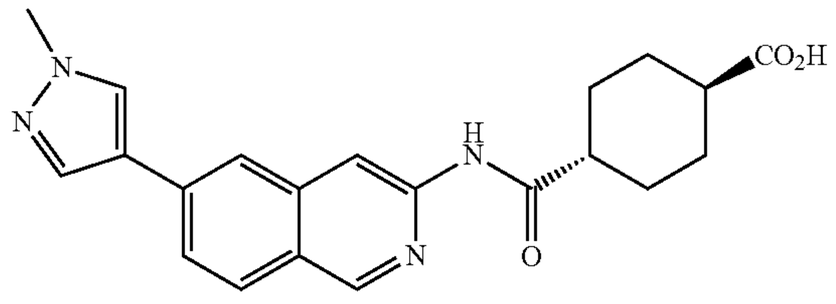

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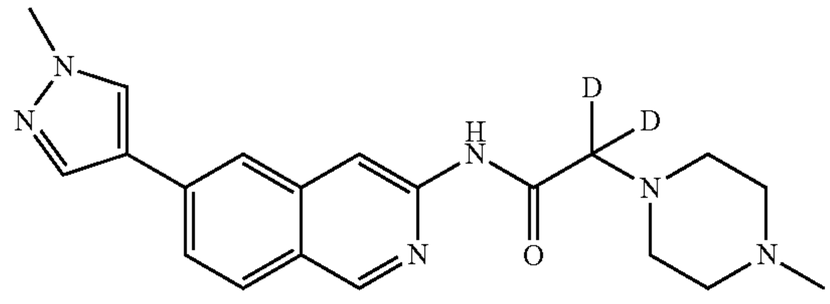

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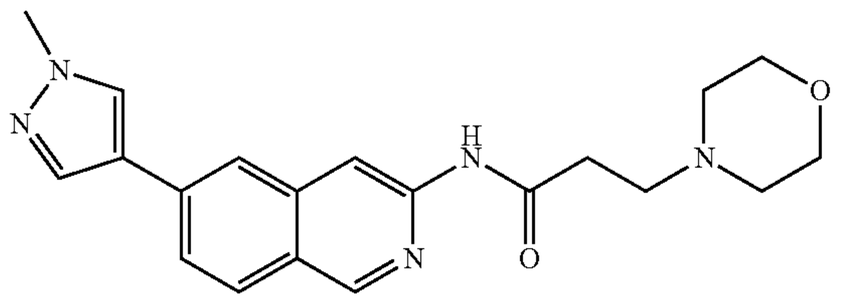

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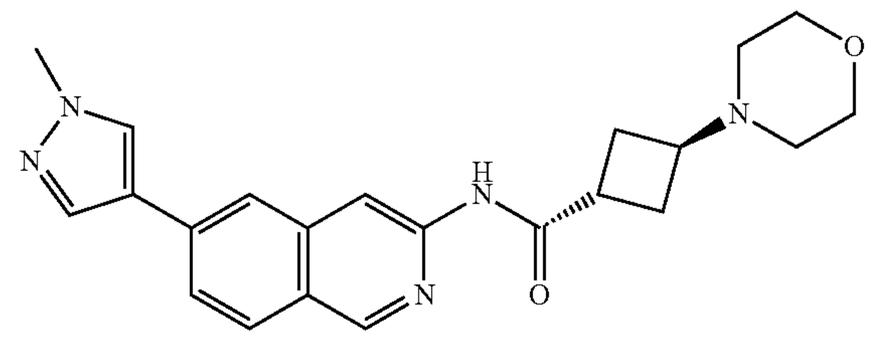

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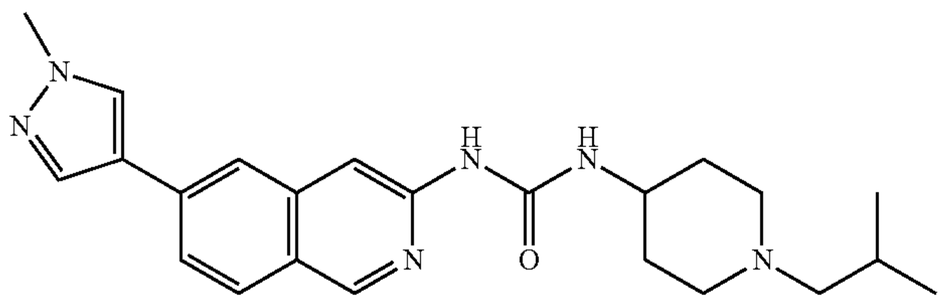

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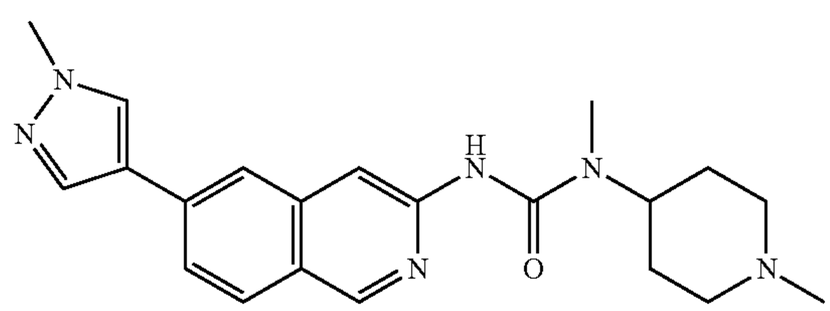

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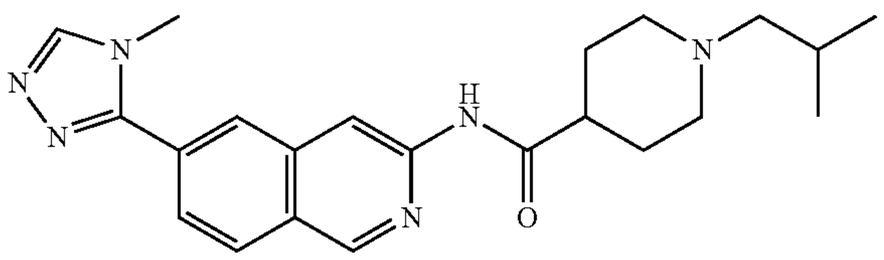

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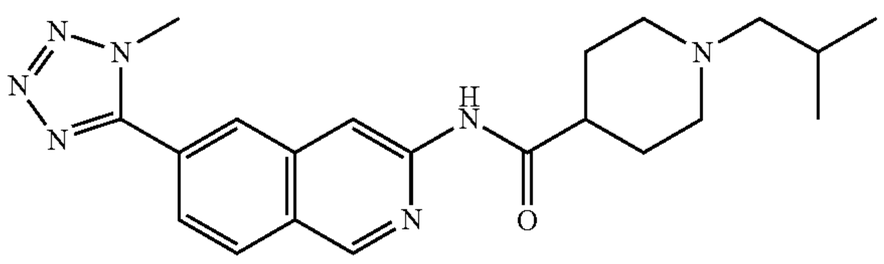

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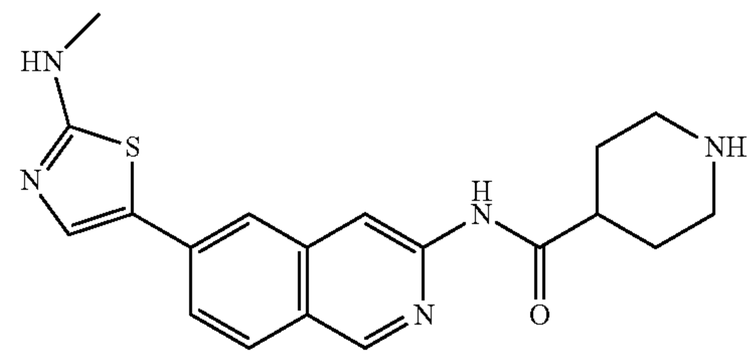
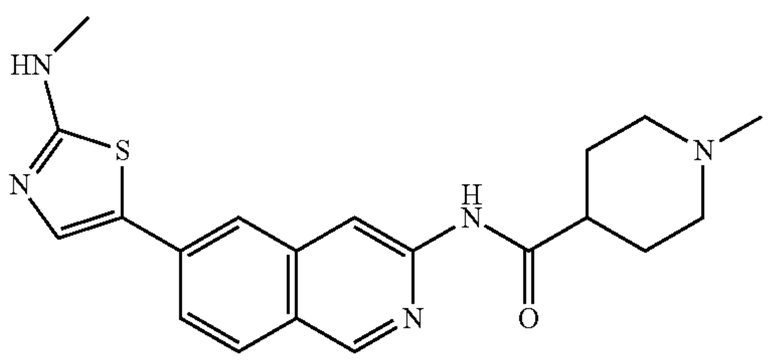
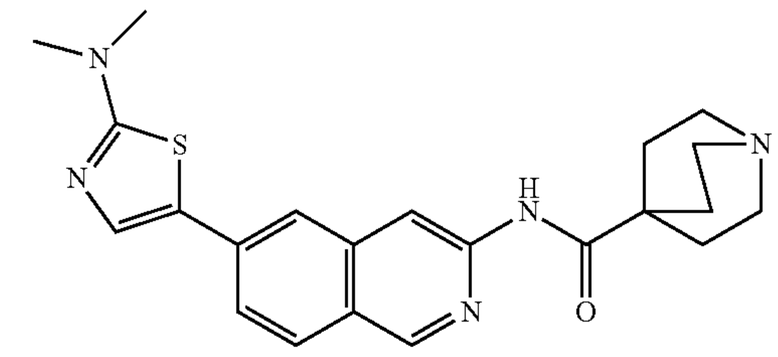
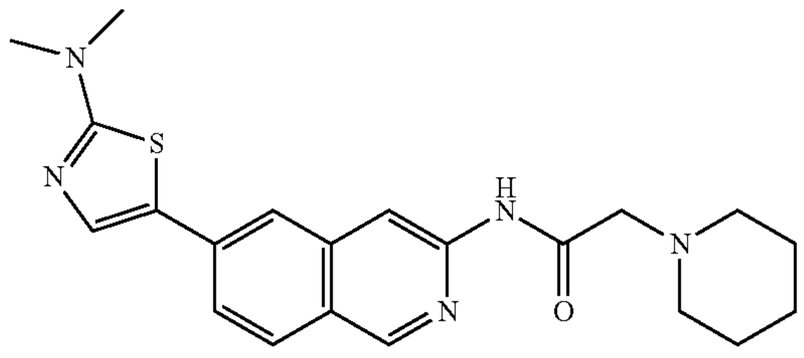
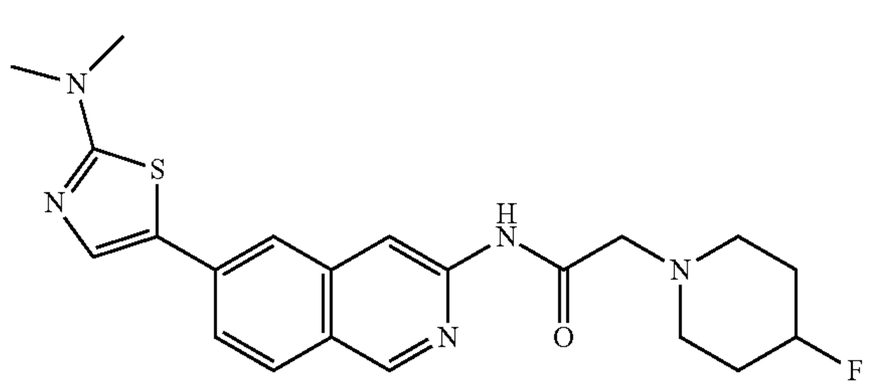
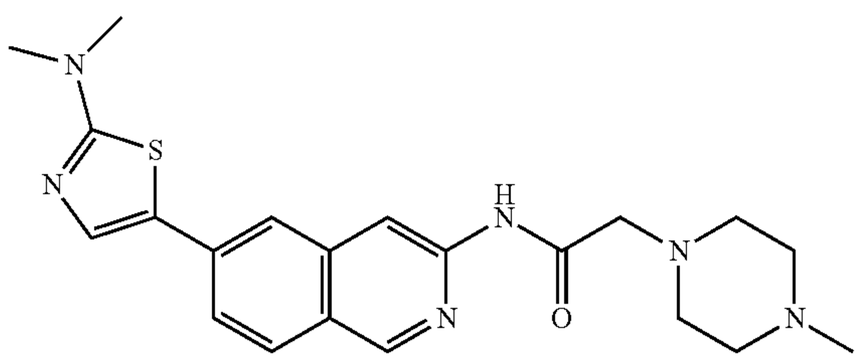
	1040
	1041
	1042
	1043
	1044
	1045

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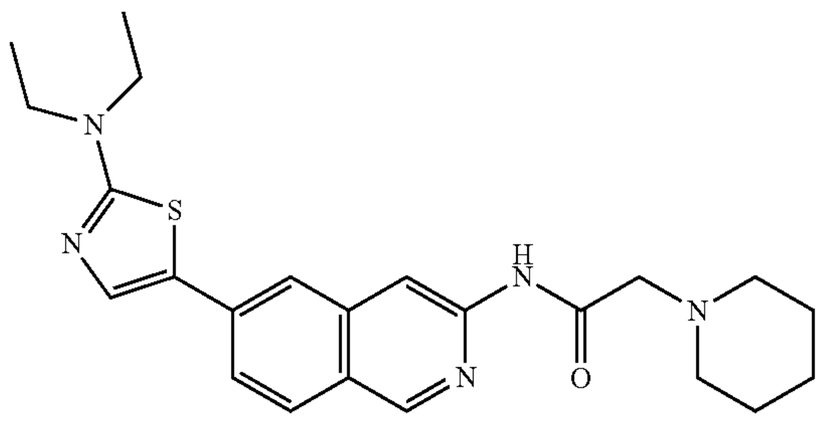
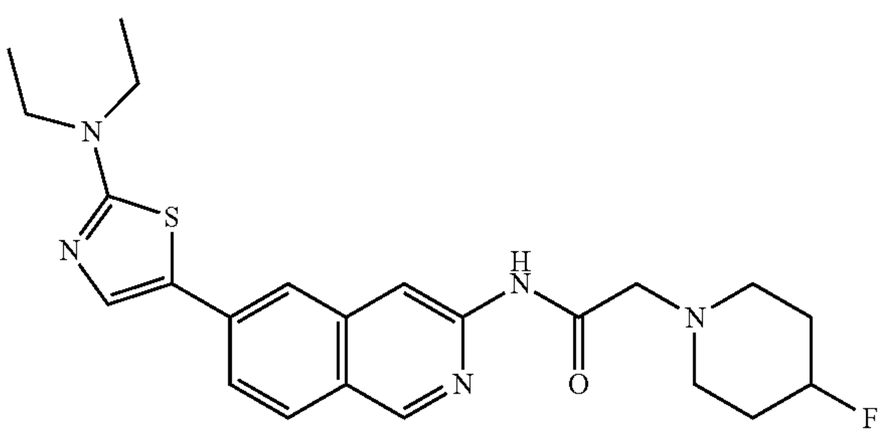
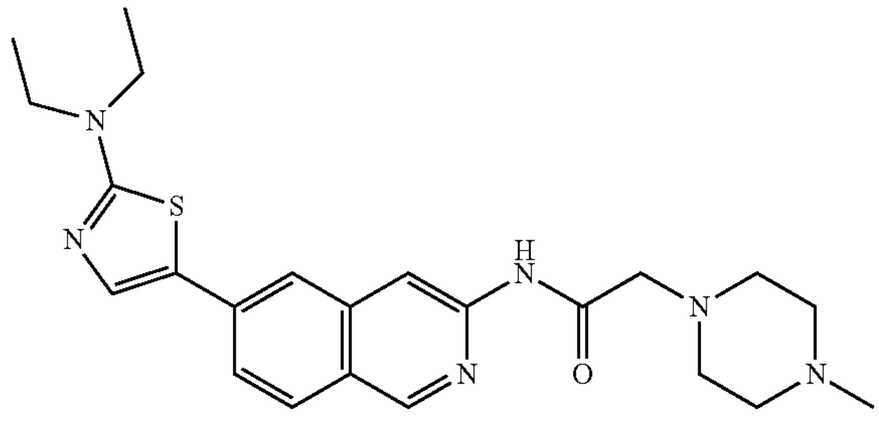
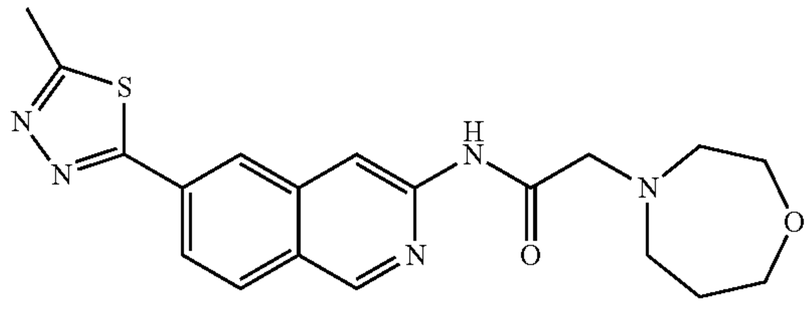
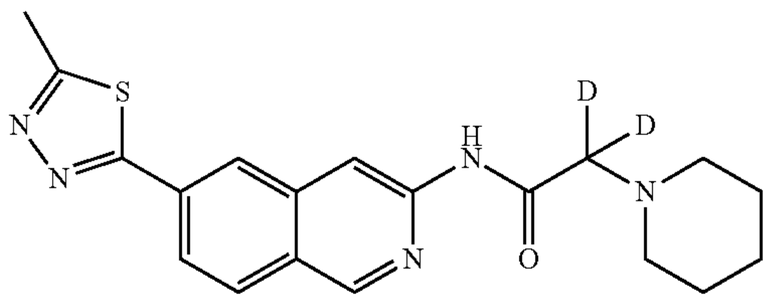
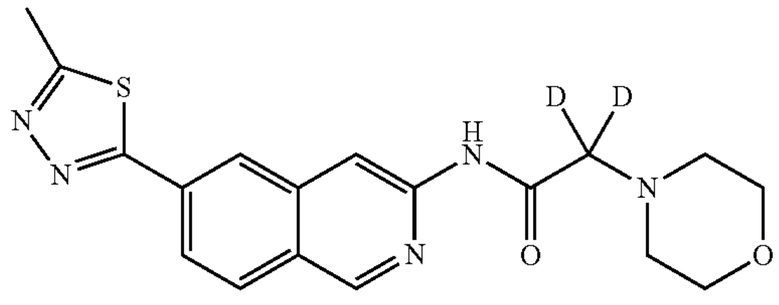
1046	
1047	
1048	
1049	
1050	
1051	

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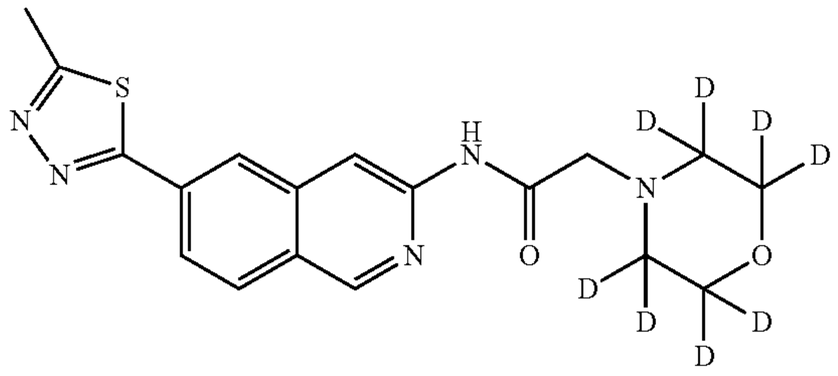
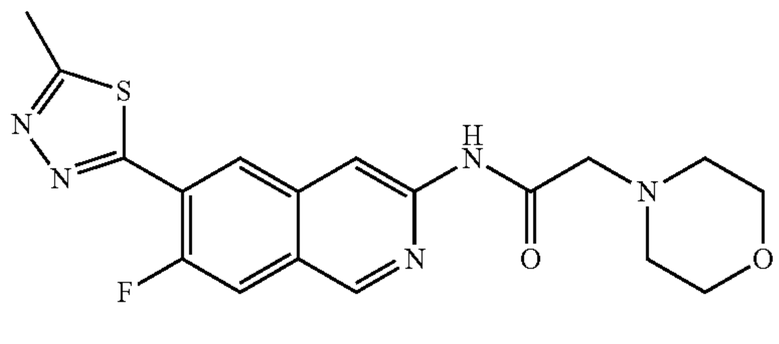
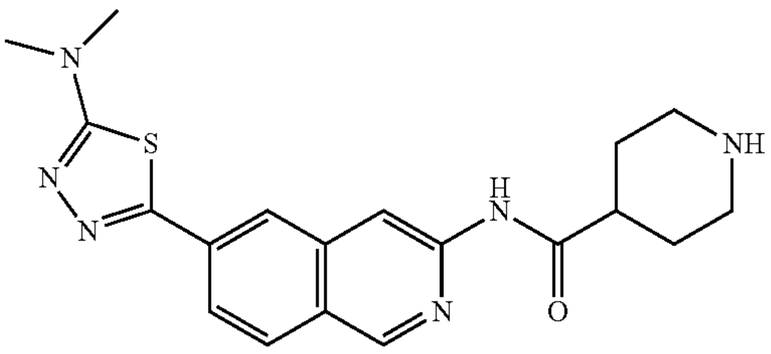
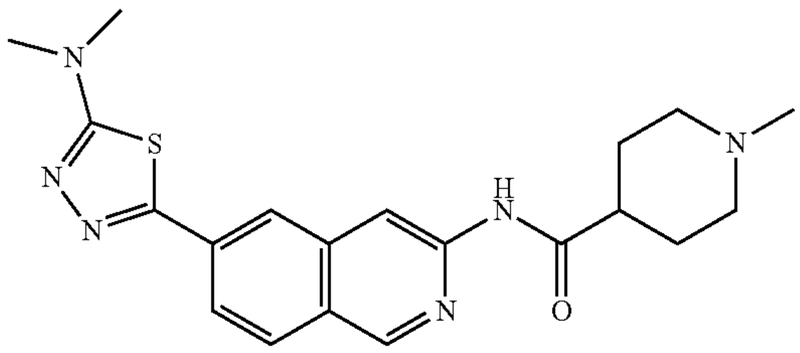
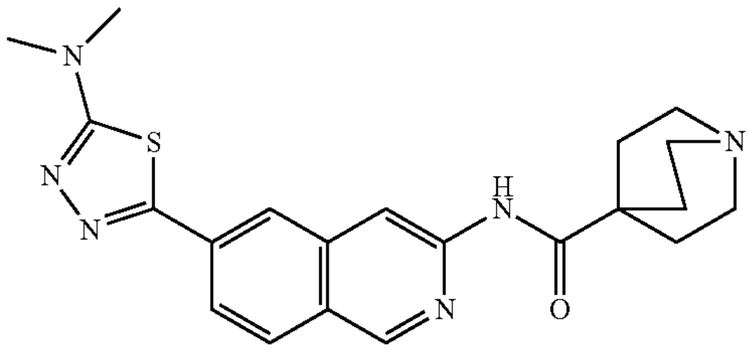
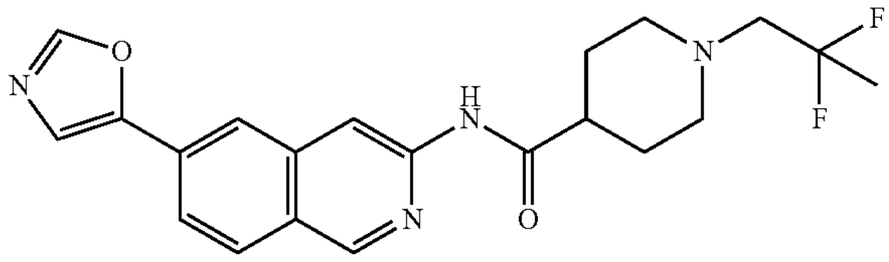
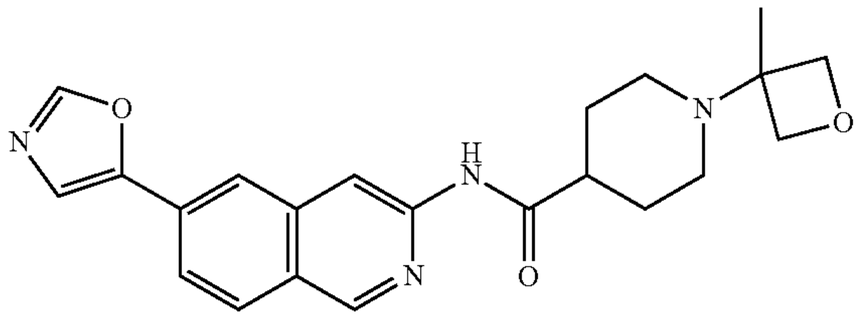
	1052
	1053
	1054
	1055
	1056
	1057
	1058

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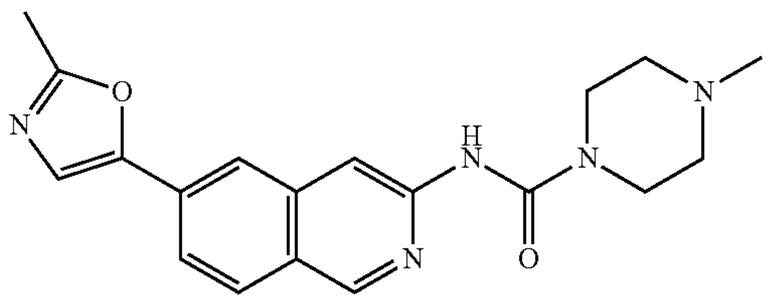
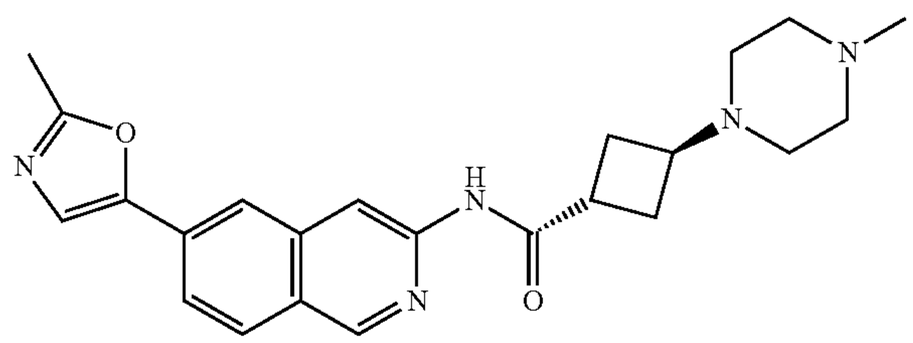
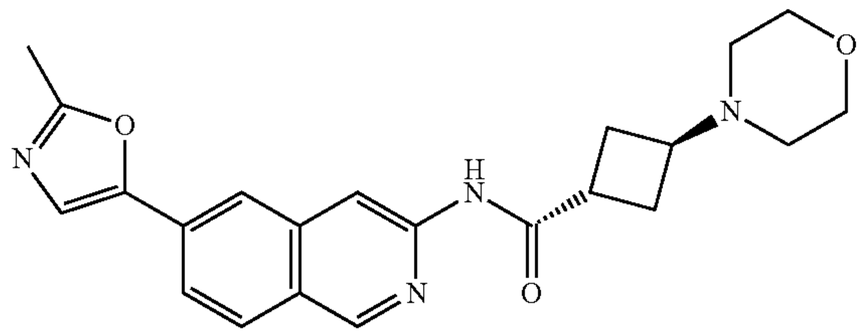
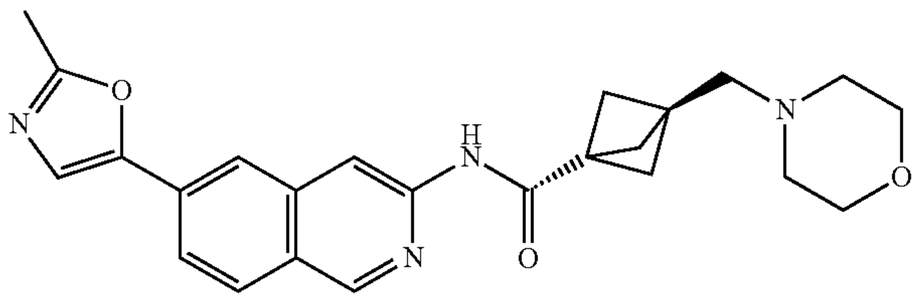
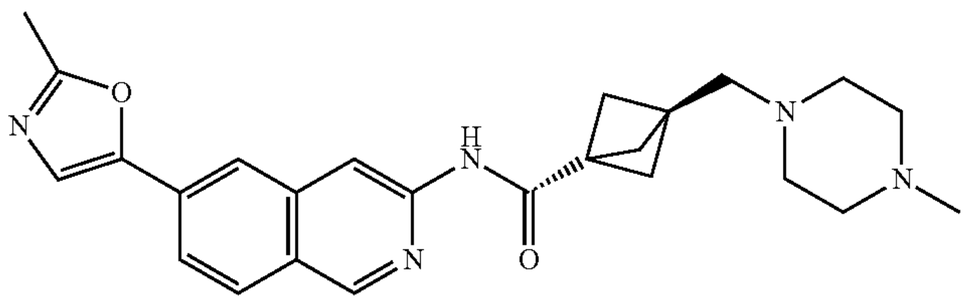
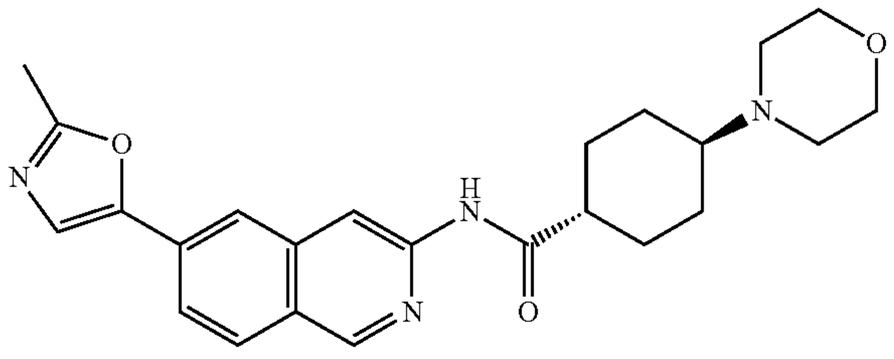
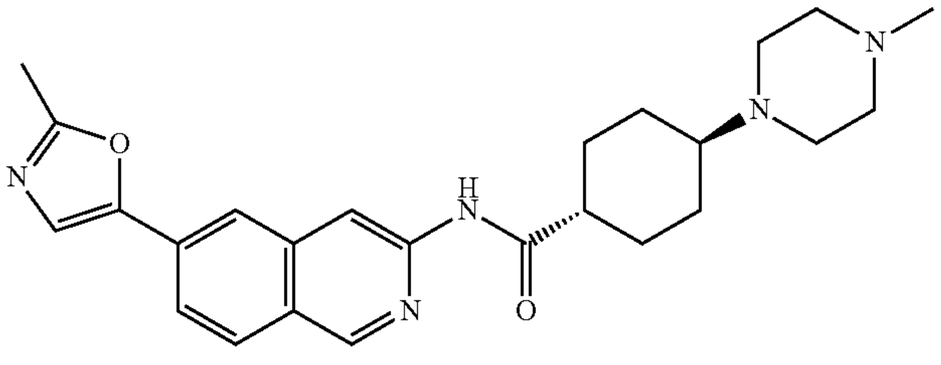
1059	
1060	
1061	
1062	
1063	
1064	
1065	

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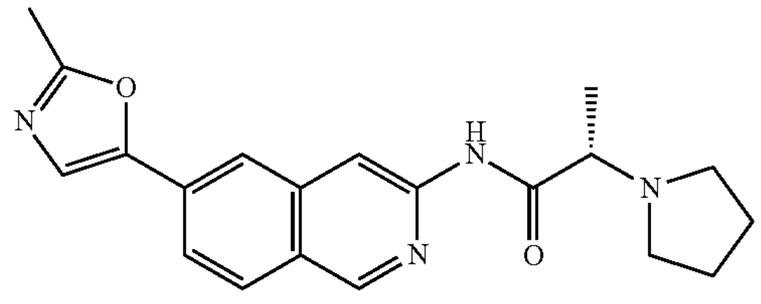
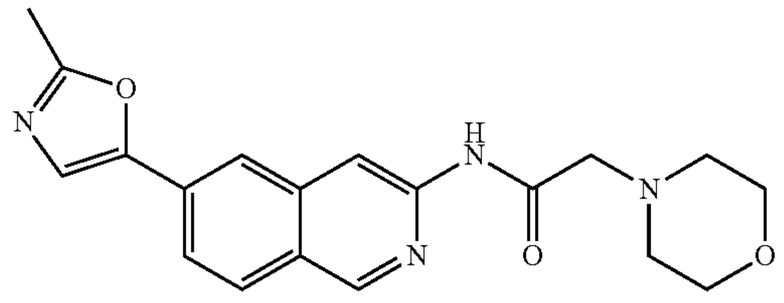
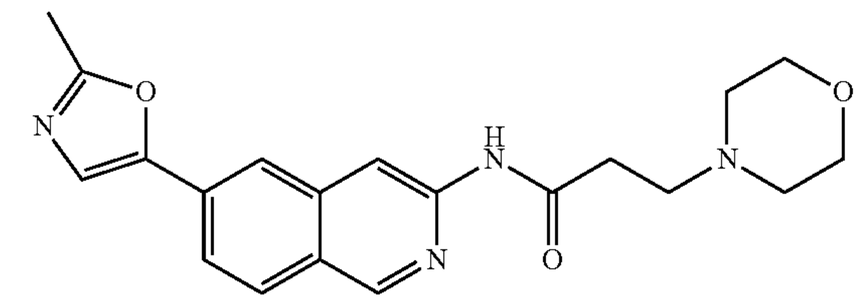
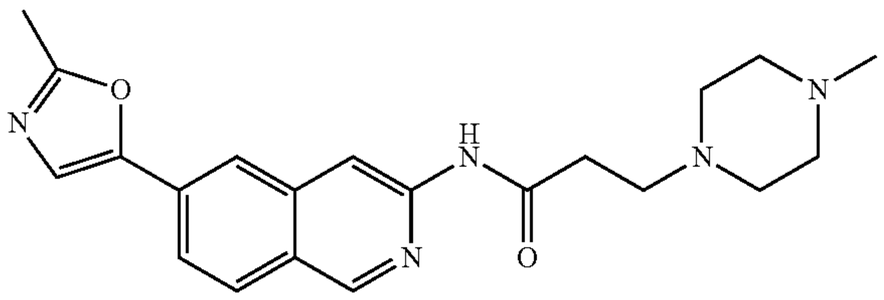
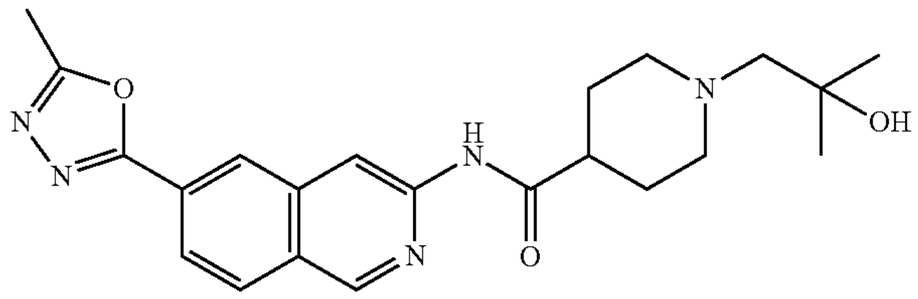
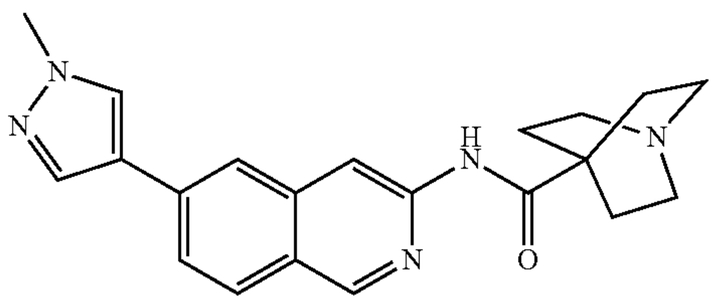
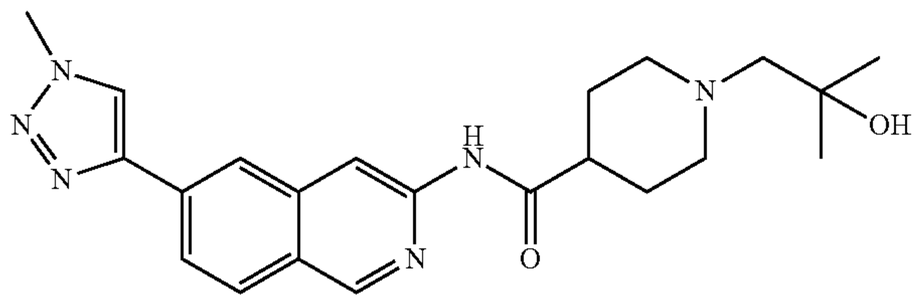
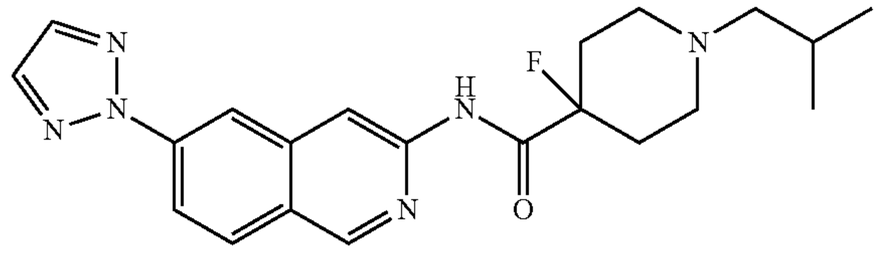
	1066
	1067
	1068
	1069
	1070
	1071
	1072
	1073

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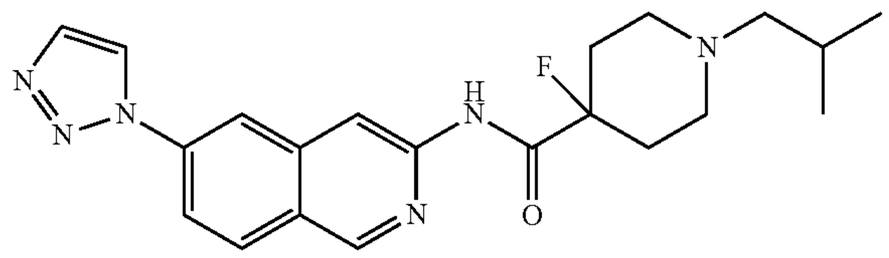
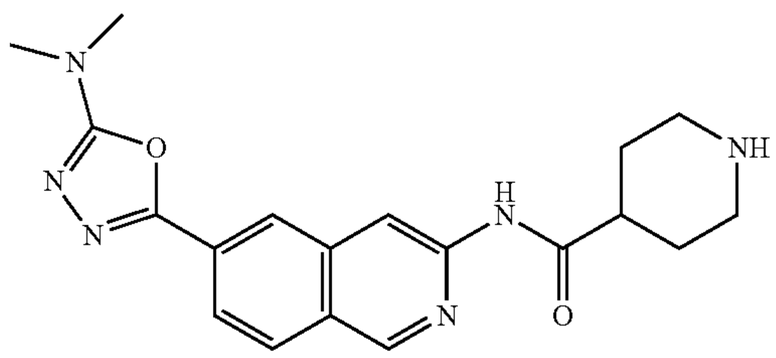
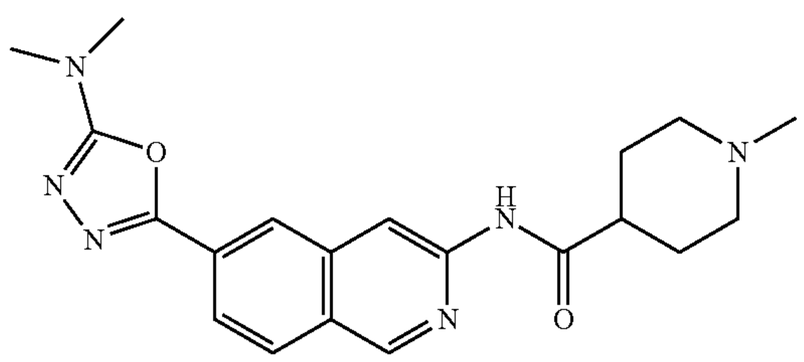
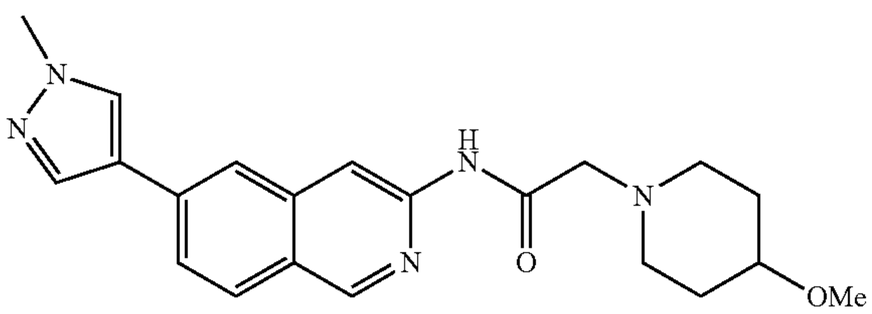
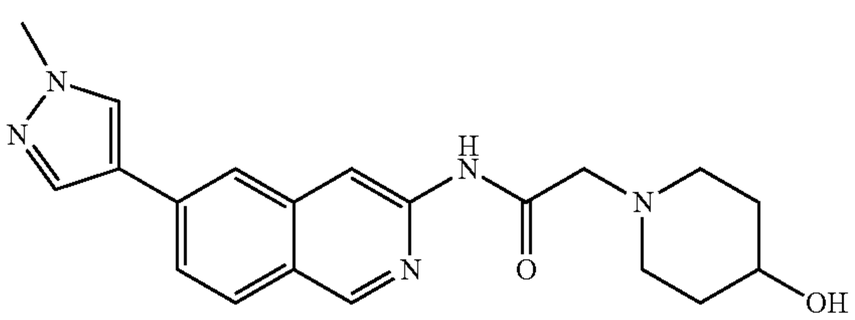
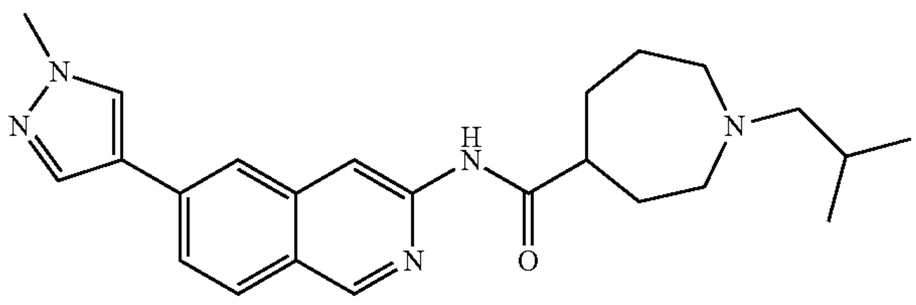
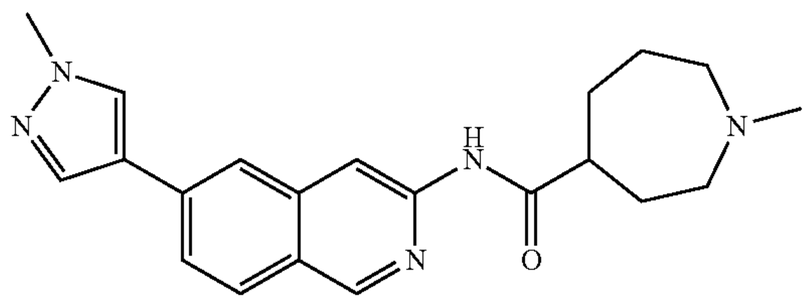
	1074
	1075
	1076
	1077
	1078
	1079
	1080

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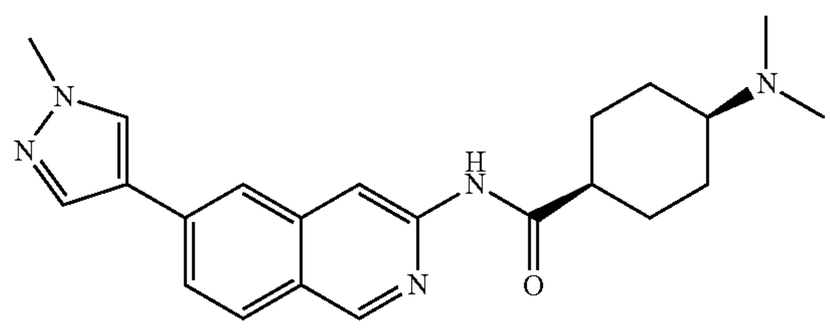
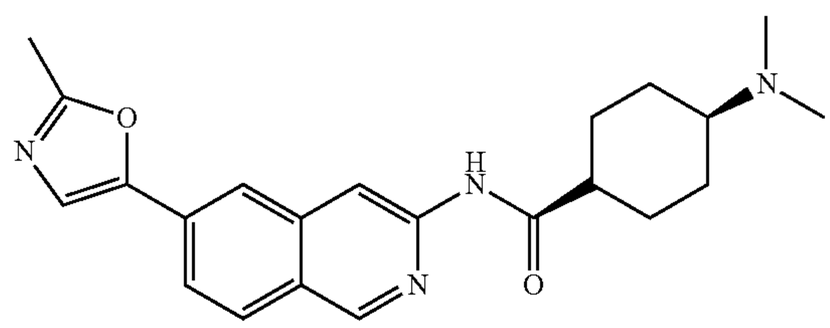
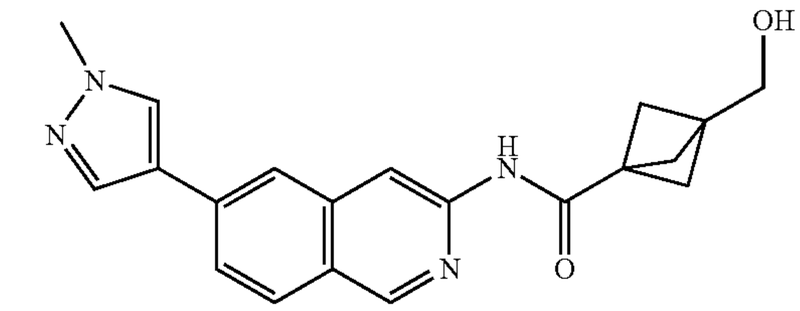
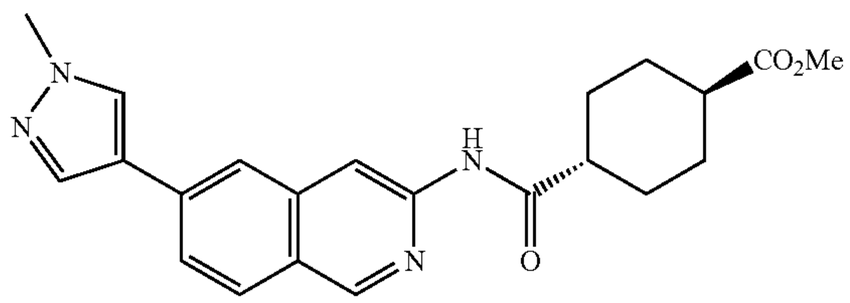
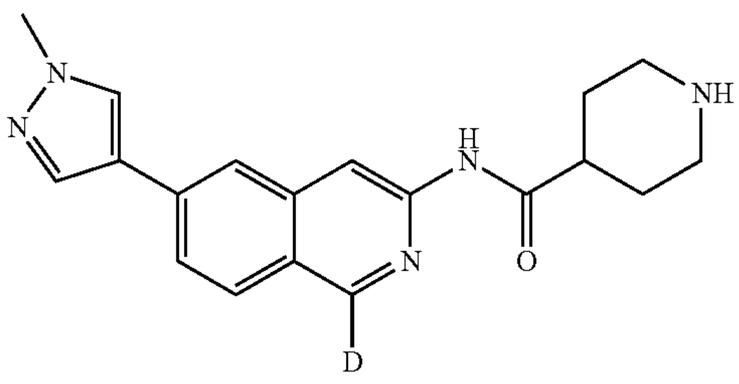
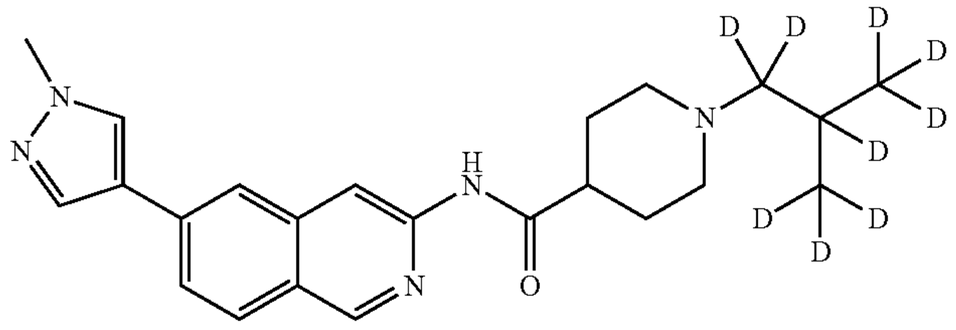
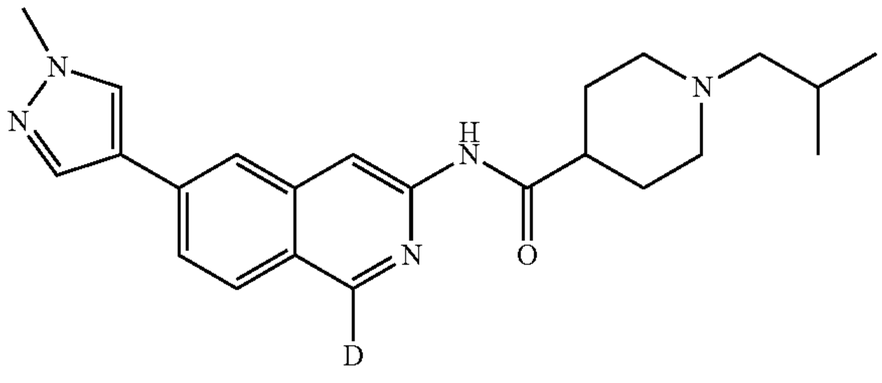
	1081
	1082
	1083
	1084
	1085
	1086
	1087

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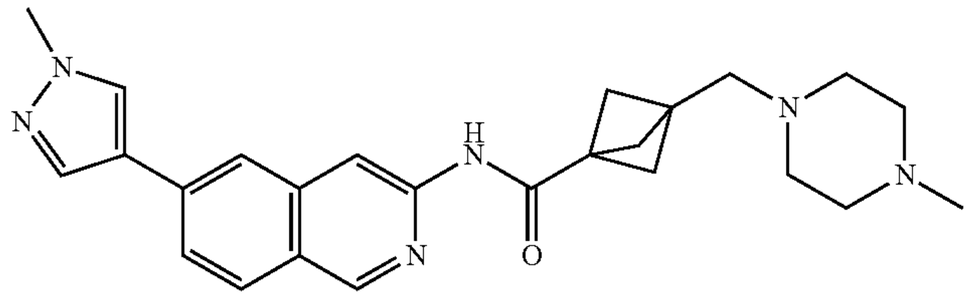
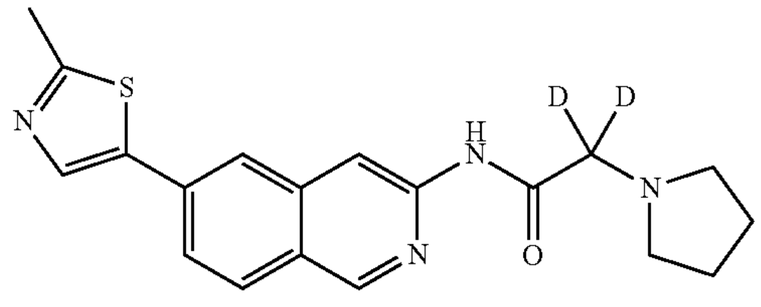
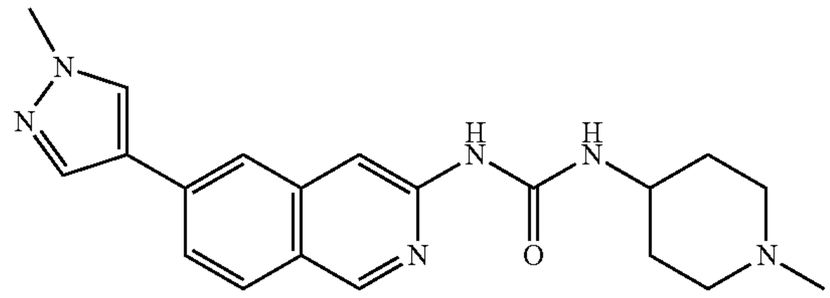
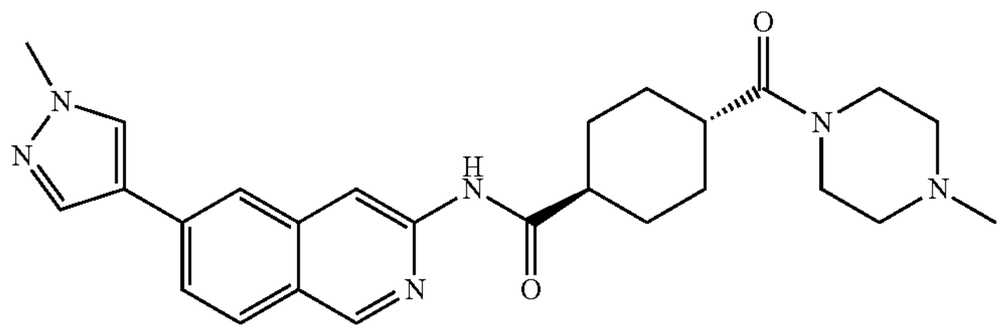
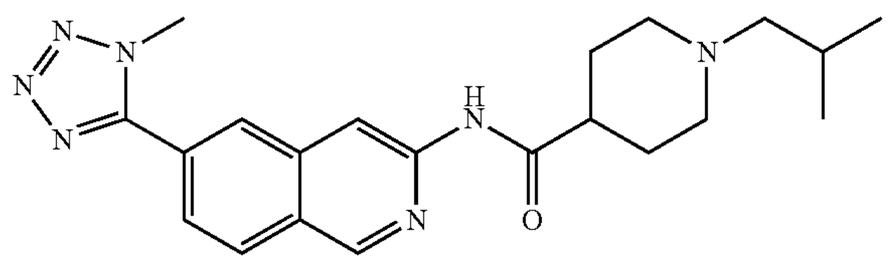
	1088 
	1089 
	1090 
	1091 
	1092 

Administration and Pharmaceutical Compositions

Some embodiments include pharmaceutical compositions comprising: (a) a therapeutically effective amount of a compound provided herein, or its corresponding enantiomer, diastereoisomer or tautomer, or pharmaceutically acceptable salt; and (b) a pharmaceutically acceptable carrier.

The compounds provided herein may also be useful in combination (administered together or sequentially) with other known agents.

Non-limiting examples of diseases which can be treated with a combination of a compound of Formula (I) and other another active agent are colorectal cancer, ovarian cancer, chronic inflammation, diabetic retinopathy, pulmonary fibrosis, and osteoarthritis. For example, a compound of Formula (I) can be combined with one or more chemotherapeutic compounds.

In some embodiments, colorectal cancer can be treated with a combination of a compound of Formula (I) and one or more of the following drugs: 5-Fluorouracil (5-FU), which can be administered with the vitamin-like drug leucovorin (also called folinic acid); capecitabine (XELODA®), irinotecan (CAMPOSTAR®), oxaliplatin (ELOXATIN®). Examples of combinations of these drugs which could be further combined with a compound of Formula (I) are FOLFOX (5-FU, leucovorin, and oxaliplatin), FOLFIRI (5-FU, leucovorin, and irinotecan), FOLFOXIRI (leucovorin, 5-FU, oxaliplatin, and irinotecan) and CapeOx (Capecitabine and oxaliplatin). For rectal cancer, chemo with 5-FU or capecitabine combined with radiation may be given before surgery (neoadjuvant treatment).

In some embodiments, ovarian cancer can be treated with a combination of a compound of Formula (I) and one or more of the following drugs: Topotecan, Liposomal doxorubicin (DOXIL®), Gemcitabine (GEMZAR®), Cyclophosphamide (CYTOXAN®), Vinorelbine (NAVELBINE®), Ifosfamide (IFEX®), Etoposide (VP-16), Altretamine (HEXALEN®), Capecitabine (XELODA®), Irinotecan (CPT-11, CAMPTOSAR®), Melphalan, Pemetrexed (ALIMTA®) and Albumin bound paclitaxel (nab-paclitaxel, ABRAXANE®). Examples of combinations of these drugs which could be further combined with a compound of Formula (I) are TIP (paclitaxel [Taxol], ifosfamide, and cisplatin), VeIP (vinblastine, ifosfamide, and cisplatin) and VIP (etoposide [VP-16], ifosfamide, and cisplatin).

In some embodiments, a compound of Formula (I) can be used to treat cancer in combination with any of the following methods: (a) Hormone therapy such as aromatase inhibitors, LHRH [luteinizing hormone-releasing hormone] analogs

and inhibitors, and others; (b) Ablation or embolization procedures such as radiofrequency ablation (RFA), ethanol (alcohol) ablation, microwave thermotherapy and cryosurgery (cryotherapy); (c) Chemotherapy using alkylating agents such as cisplatin and carboplatin, oxaliplatin, mechlorethamine, cyclophosphamide, chlorambucil and ifosfamide; (d) Chemotherapy using anti-metabolites such as azathioprine and mercaptopurine; (e) Chemotherapy using plant alkaloids and terpenoids such as vinca alkaloids (i.e. Vincristine, Vinblastine, Vinorelbine and Vindesine) and taxanes; (f) Chemotherapy using podophyllotoxin, etoposide, teniposide and docetaxel; (g) Chemotherapy using topoisomerase inhibitors such as irinotecan, topotecan, amsacrine, etoposide, etoposide phosphate, and teniposide; (h) Chemotherapy using cytotoxic antibiotics such as actinomycin, anthracyclines, doxorubicin, daunorubicin, valrubicin, idarubicin, epirubicin, bleomycin, plicamycin and mitomycin; (i) Chemotherapy using tyrosine-kinase inhibitors such as Imatinib mesylate (GLEEVEC®, also known as STI-571), Gefitinib (Iressa, also known as ZD1839), Erlotinib (marketed as TARCEVA®), Bortezomib (VELCADE®), tamoxifen, tofacitinib, crizotinib, Bcl-2 inhibitors (e.g. obatoclax in clinical trials, ABT-263, and Gossypol), PARP inhibitors (e.g. Iniparib, Olaparib in clinical trials), PI3K inhibitors (e.g. perifosine in a phase III trial), VEGF Receptor 2 inhibitors (e.g. Apatinib), AN-152, (AEZS-108), Braf inhibitors (e.g. vemurafenib, dabrafenib and LGX818), MEK inhibitors (e.g. trametinib and MEK162), CDK inhibitors, (e.g. PD-0332991), salinomycin and Sorafenib; (j) Chemotherapy using monoclonal antibodies such as Rituximab (marketed as MABTHERA® or RITUXAN®), Trastuzumab (Herceptin also known as ErbB2), Cetuximab (marketed as ERBITUX®), and Bevacizumab (marketed asAVASTIN®); and (k) radiation therapy.

In some embodiments, diabetic retinopathy can be treated with a combination of a compound of Formula (I) and one or more of the following natural supplements: Bilberry, Butcher's broom, Ginkgo, Grape seed extract, and Pycnogenol (Pine bark).

In some embodiments, idiopathic pulmonary fibrosis/pulmonary fibrosis can be treated with a combination of a compound of Formula (I) and one or more of the following drugs: pirfenidone (pirfenidone was approved for use in 2011 in Europe under the brand name Esbriet®), prednisone, azathioprine, N-acetylcysteine, interferon-γ 1b, bosentan (bosentan is currently being studied in patients with IPF, [*The American Journal of Respiratory and Critical Care Medicine* (2011), 184(1), 92-9]), Nintedanib (BIBF 1120 and Vargatef), QAX576 [*British Journal of Pharmacology* (2011), 163(1), 141-172], and anti-inflammatory agents such as corticosteroids.

In some embodiments, a compound of Formula (I) can be used to treat idiopathic pulmonary fibrosis/pulmonary fibrosis in combination with any of the following methods: oxygen therapy, pulmonary rehabilitation and surgery.

In some embodiments, a compound of Formula (I) can be used to treat osteoarthritis in combination with any of the following methods: (a) Nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen, naproxen, aspirin and acetaminophen; (b) physical therapy; (c) injections of corticosteroid medications; (d) injections of hyaluronic acid derivatives (e.g. Hyalgan, Synvisc); (e) narcotics, like codeine; (f) in combination with braces and/or shoe inserts or any device that can immobilize or support your joint to help you keep pressure off it (e.g., splints, braces, shoe inserts or other medical devices); (g) realigning bones (osteotomy); (h) joint replacement (arthroplasty); and (i) in combination with a chronic pain class.

In some embodiments, macular degeneration can be treated with a combination of a compound of Formula (I) and one or more of the following drugs: Bevacizumab (Avastin®), Ranibizumab (Lucentis®), Pegaptanib (Macugen), Aflibercept (Eylea®), verteporfin (Visudyne®) in combination with photodynamic therapy (PDT) or with any of the following methods: (a) in combination with laser to destroy abnormal blood vessels (photocoagulation); and (b) in combination with increased vitamin intake of antioxidant vitamins and zinc.

In some embodiments, retinitis pigmentosa can be treated with a combination of a compound of Formula (I) and one or more of the following drugs: UF-021 (Ocuseva™) vitamin A palmitate and pikachurin or with any of the following methods: (a) with the Argus® II retinal implant; and (b) with stem cell and/or gene therapy.

Administration of the compounds disclosed herein or the pharmaceutically acceptable salts thereof can be via any of the accepted modes of administration, including, but not limited to, orally, subcutaneously, intravenously, intranasally, topically, transdermally, intraperitoneally, intramuscularly, intrapulmonarilly, vaginally, rectally, ontologically, neuro-otologically, intraocularly, subconjuctivally, via anterior eye chamber injection, intravitreally, intraperitoneally, intrathecally, intracystically, intrapleurally, via wound irrigation, intrabuccally, intra-abdominally, intra-articularly, intra-aurally, intrabronchially, intracapsularly, intrameningeally, via inhalation, via endotracheal or endobronchial instillation, via direct instillation into pulmonary cavities, intraspinally, intrasynovially, intrathoracically, via thoracostomy irrigation, epidurally, intratympanically, intracisternally, intravascularly, intraventricularly, intraosseously, via irrigation of infected bone, or via application as part of any admixture with a prosthetic devices. In some embodiments, the administration method includes oral or parenteral administration.

Compounds provided herein intended for pharmaceutical use may be administered as crystalline or amorphous products. Pharmaceutically acceptable compositions may include solid, semi-solid, liquid, solutions, colloidal, liposomes, emulsions, suspensions, complexes, coacervates and aerosols. Dosage forms, such as, e.g., tablets, capsules, powders, liquids, suspensions, suppositories, aerosols, implants, controlled release or the like. They may be obtained, for example, as solid plugs, powders, or films by methods such as precipitation, crystallization, milling, grinding, supercritical fluid processing, coacervation, complex coacervation, encapsulation, emulsification, complexation, freeze drying, spray drying, or evaporative drying. Microwave or radio frequency drying may be used for this purpose. The compounds can also be administered in sustained or controlled release dosage forms, including depot injections, osmotic pumps, pills (tablets and or capsules), transdermal (including electrotransport) patches, implants and the like, for prolonged and/or timed, pulsed administration at a predetermined rate.

The compounds can be administered either alone or in combination with a conventional pharmaceutical carrier, excipient or the like. Pharmaceutically acceptable excipients include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, self-emulsifying drug delivery systems (SEDDS) such as d-α-tocopherol polyethylene glycol 1000 succinate, surfactants used in pharmaceutical dosage forms such as Tweens, poloxamers or other similar polymeric delivery matrices, serum proteins, such as human

serum albumin, buffer substances such as phosphates, tris, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium-chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethyl cellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, and wool fat. Cyclodextrins such as α-, β, and γ-cyclodextrin, or chemically modified derivatives such as hydroxyalkylcyclodextrins, including 2- and 3-hydroxypropyl-β-cyclodextrins, or other solubilized derivatives can also be used to enhance delivery of compounds described herein. Dosage forms or compositions containing a compound as described herein in the range of 0.005% to 100% with the balance made up from non-toxic carrier may be prepared. The contemplated compositions may contain 0.001%-100% of a compound provided herein, in one embodiment 0.1-95%, in another embodiment 75-85%, in a further embodiment 20-80%. Actual methods of preparing such dosage forms are known, or will be apparent, to those skilled in this art; for example, see *Remington: The Science and Practice of Pharmacy,* 22nd Edition (Pharmaceutical Press, London, UK. 2012).

In one embodiment, the compositions will take the form of a unit dosage form such as a pill or tablet and thus the composition may contain, along with a compound provided herein, a diluent such as lactose, sucrose, dicalcium phosphate, or the like; a lubricant such as magnesium stearate or the like; and a binder such as starch, gum acacia, polyvinylpyrrolidine, gelatin, cellulose, cellulose derivatives or the like. In another solid dosage form, a powder, marume, solution or suspension (e.g., in propylene carbonate, vegetable oils, PEG's, poloxamer 124 or triglycerides) is encapsulated in a capsule (gelatin or cellulose base capsule). Unit dosage forms in which one or more compounds provided herein or additional active agents are physically separated are also contemplated; e.g., capsules with granules (or tablets in a capsule) of each drug; two-layer tablets; two-compartment gel caps, etc. Enteric coated or delayed release oral dosage forms are also contemplated.

Liquid pharmaceutically administrable compositions can, for example, be prepared by dissolving, dispersing, etc. a compound provided herein and optional pharmaceutical adjuvants in a carrier (e.g., water, saline, aqueous dextrose, glycerol, glycols, ethanol or the like) to form a solution, colloid, liposome, emulsion, complexes, coacervate or suspension. If desired, the pharmaceutical composition can also contain minor amounts of nontoxic auxiliary substances such as wetting agents, emulsifying agents, co-solvents, solubilizing agents, pH buffering agents and the like (e.g., sodium acetate, sodium citrate, cyclodextrin derivatives, sorbitan monolaurate, triethanolamine acetate, triethanolamine oleate, and the like).

In some embodiments, the unit dosage of compounds of Formula (I) is about 0.25 mg/Kg to about 50 mg/Kg in humans.

In some embodiments, the unit dosage of compounds of Formula (I) is about 0.25 mg/Kg to about 20 mg/Kg in humans.

In some embodiments, the unit dosage of compounds of Formula (I) is about 0.50 mg/Kg to about 19 mg/Kg in humans.

In some embodiments, the unit dosage of compounds of Formula (I) is about 0.75 mg/Kg to about 18 mg/Kg in humans.

In some embodiments, the unit dosage of compounds of Formula (I) is about 1.0 mg/Kg to about 17 mg/Kg in humans.

In some embodiments, the unit dosage of compounds of Formula (I) is about 1.25 mg/Kg to about 16 mg/Kg in humans.

In some embodiments, the unit dosage of compounds of Formula (I) is about 1.50 mg/Kg to about 15 mg/Kg in humans.

In some embodiments, the unit dosage of compounds of Formula (I) is about 1.75 mg/Kg to about 14 mg/Kg in humans.

In some embodiments, the unit dosage of compounds of Formula (I) is about 2.0 mg/Kg to about 13 mg/Kg in humans.

In some embodiments, the unit dosage of compounds of Formula (I) is about 3.0 mg/Kg to about 12 mg/Kg in humans.

In some embodiments, the unit dosage of compounds of Formula (I) is about 4.0 mg/Kg to about 11 mg/Kg in humans.

In some embodiments, the unit dosage of compounds of Formula (I) is about 5.0 mg/Kg to about 10 mg/Kg in humans.

In some embodiments, the compositions are provided in unit dosage forms suitable for single administration.

In some embodiments, the compositions are provided in unit dosage forms suitable for twice a day administration.

In some embodiments, the compositions are provided in unit dosage forms suitable for three times a day administration.

Injectables can be prepared in conventional forms, either as liquid solutions, colloid, liposomes, complexes, coacervate or suspensions, as emulsions, or in solid forms suitable for reconstitution in liquid prior to injection. The percentage of a compound provided herein contained in such parenteral compositions is highly dependent on the specific nature thereof, as well as the activity of the compound and the needs of the patient. However, percentages of active ingredient of 0.01% to 10% in solution are employable, and could be higher if the composition is a solid or suspension, which could be subsequently diluted to the above percentages.

In some embodiments, the composition will comprise about 0.1-10% of the active agent in solution.

In some embodiments, the composition will comprise about 0.1-5% of the active agent in solution.

In some embodiments, the composition will comprise about 0.1-4% of the active agent in solution.

In some embodiments, the composition will comprise about 0.15-3% of the active agent in solution.

In some embodiments, the composition will comprise about 0.2-2% of the active agent in solution.

In some embodiments, the compositions are provided in dosage forms suitable for continuous dosage by intravenous infusion over a period of about 1-96 hours.

In some embodiments, the compositions are provided in dosage forms suitable for continuous dosage by intravenous infusion over a period of about 1-72 hours.

In some embodiments, the compositions are provided in dosage forms suitable for continuous dosage by intravenous infusion over a period of about 1-48 hours.

In some embodiments, the compositions are provided in dosage forms suitable for continuous dosage by intravenous infusion over a period of about 1-24 hours.

In some embodiments, the compositions are provided in dosage forms suitable for continuous dosage by intravenous infusion over a period of about 1-12 hours.

In some embodiments, the compositions are provided in dosage forms suitable for continuous dosage by intravenous infusion over a period of about 1-6 hours.

In some embodiments, these compositions can be administered by intravenous infusion to humans at doses of about 5 mg/m^2 to about 300 mg/m^2.

In some embodiments, these compositions can be administered by intravenous infusion to humans at doses of about 5 mg/m^2 to about 200 mg/m^2.

In some embodiments, these compositions can be administered by intravenous infusion to humans at doses of about 5 mg/m^2 to about 100 mg/m^2.

In some embodiments, these compositions can be administered by intravenous infusion to humans at doses of about 10 mg/m^2 to about 50 mg/m^2.

In some embodiments, these compositions can be administered by intravenous infusion to humans at doses of about 50 mg/m^2 to about 200 mg/m^2.

In some embodiments, these compositions can be administered by intravenous infusion to humans at doses of about 75 mg/m^2 to about 175 mg/m^2.

In some embodiments, these compositions can be administered by intravenous infusion to humans at doses of about 100 mg/m^2 to about 150 mg/m^2.

It is to be noted that concentrations and dosage values may also vary depending on the specific compound and the severity of the condition to be alleviated. It is to be further understood that for any particular patient, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions, and that the concentration ranges set forth herein are exemplary only and are not intended to limit the scope or practice of the claimed compositions.

In one embodiment, the compositions can be administered to the respiratory tract (including nasal and pulmonary) e.g., through a nebulizer, metered-dose inhalers, atomizer, mister, aerosol, dry powder inhaler, insufflator, liquid instillation or other suitable device or technique.

In some embodiments, aerosols intended for delivery to the nasal mucosa are provided for inhalation through the nose. For optimal delivery to the nasal cavities, inhaled particle sizes of about 5 to about 100 microns are useful, with particle sizes of about 10 to about 60 microns being preferred. For nasal delivery, a larger inhaled particle size may be desired to maximize impaction on the nasal mucosa and to minimize or prevent pulmonary deposition of the administered formulation. In some embodiments, aerosols intended for delivery to the lung are provided for inhalation through the nose or the mouth. For delivery to the lung, inhaled aerodynamic particle sizes of about less than 10 μm are useful (e.g., about 1 to about 10 microns). Inhaled particles may be defined as liquid droplets containing dissolved drug, liquid droplets containing suspended drug particles (in cases where the drug is insoluble in the suspending medium), dry particles of pure drug substance, drug substance incorporated with excipients, liposomes, emulsions, colloidal systems, coacervates, aggregates of drug nanoparticles, or dry particles of a diluent which contain embedded drug nanoparticles.

In some embodiments, compounds of Formula (I) disclosed herein intended for respiratory delivery (either systemic or local) can be administered as aqueous formulations, as non-aqueous solutions or suspensions, as suspensions or solutions in halogenated hydrocarbon propellants with or without alcohol, as a colloidal system, as emulsions, coacervates, or as dry powders. Aqueous formulations may be aerosolized by liquid nebulizers employing either hydraulic or ultrasonic atomization or by modified micropump systems (like the soft mist inhalers, the Aerodose® or the AERx® systems). Propellant-based systems may use suitable pressurized metered-dose inhalers (pMDIs). Dry powders may use dry powder inhaler devices (DPIs), which are capable of dispersing the drug substance effectively. A desired particle size and distribution may be obtained by choosing an appropriate device.

In some embodiments, the compositions of Formula (I) disclosed herein can be administered to the ear by various methods. For example, a round window catheter (e.g., U.S. Pat. Nos. 6,440,102 and 6,648,873) can be used.

Alternatively, formulations can be incorporated into a wick for use between the outer and middle ear (e.g., U.S. Pat. No. 6,120,484) or absorbed to collagen sponge or other solid support (e.g., U.S. Pat. No. 4,164,559).

If desired, formulations of the disclosure can be incorporated into a gel formulation (e.g., U.S. Pat. Nos. 4,474,752 and 6,911,211).

In some embodiments, compounds of Formula (I) disclosed herein intended for delivery to the ear can be administered via an implanted pump and delivery system through a needle directly into the middle or inner ear (cochlea) or through a cochlear implant stylet electrode channel or alternative prepared drug delivery channel such as but not limited to a needle through temporal bone into the cochlea.

Other options include delivery via a pump through a thin film coated onto a multichannel electrode or electrode with a specially imbedded drug delivery channel (pathways) carved into the thin film for this purpose. In other embodiments the acidic or basic solid compound of Formula (I) can be delivered from the reservoir of an external or internal implanted pumping system.

Formulations of the disclosure also can be administered to the ear by intratympanic injection into the middle ear, inner ear, or cochlea (e.g., U.S. Pat. No. 6,377,849 and Ser. No. 11/337,815).

Intratympanic injection of therapeutic agents is the technique of injecting a therapeutic agent behind the tympanic membrane into the middle and/or inner ear. In one embodiment, the formulations described herein are administered directly onto the round window membrane via transtympanic injection. In another embodiment, the ion channel modulating agent auris-acceptable formulations described herein are administered onto the round window membrane via a non-transtympanic approach to the inner ear. In additional embodiments, the formulation described herein is administered onto the round window membrane via a surgical approach to the round window membrane comprising modification of the crista fenestrae cochleae.

In some embodiments, the compounds of Formula (I) are formulated in rectal compositions such as enemas, rectal gels, rectal foams, rectal aerosols, suppositories, jelly suppositories, or retention enemas, containing conventional suppository bases such as cocoa butter or other glycerides, as well as synthetic polymers such as polyvinylpyrrolidone, PEG (like PEG ointments), and the like.

Suppositories for rectal administration of the drug (either as a solution, colloid, suspension or a complex) can be prepared by mixing a compound provided herein with a suitable non-irritating excipient that is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt or erode/dissolve in the rectum and release the compound. Such materials include cocoa butter, glycerinated gelatin, hydrogenated vegetable oils, poloxamers, mixtures of polyethylene glycols of various molecular

weights and fatty acid esters of polyethylene glycol. In suppository forms of the compositions, a low-melting wax such as, but not limited to, a mixture of fatty acid glycerides, optionally in combination with cocoa butter, is first melted.

Solid compositions can be provided in various different types of dosage forms, depending on the physicochemical properties of the compound provided herein, the desired dissolution rate, cost considerations, and other criteria. In one of the embodiments, the solid composition is a single unit. This implies that one unit dose of the compound is comprised in a single, physically shaped solid form or article. In other words, the solid composition is coherent, which is in contrast to a multiple unit dosage form, in which the units are incoherent.

Examples of single units which may be used as dosage forms for the solid composition include tablets, such as compressed tablets, film-like units, foil-like units, wafers, lyophilized matrix units, and the like. In one embodiment, the solid composition is a highly porous lyophilized form. Such lyophilizates, sometimes also called wafers or lyophilized tablets, are particularly useful for their rapid disintegration, which also enables the rapid dissolution of the compound.

On the other hand, for some applications the solid composition may also be formed as a multiple unit dosage form as defined above. Examples of multiple units are powders, granules, microparticles, pellets, mini-tablets, beads, lyophilized powders, and the like. In one embodiment, the solid composition is a lyophilized powder. Such a dispersed lyophilized system comprises a multitude of powder particles, and due to the lyophilization process used in the formation of the powder, each particle has an irregular, porous microstructure through which the powder is capable of absorbing water very rapidly, resulting in quick dissolution. Effervescent compositions are also contemplated to aid the quick dispersion and absorption of the compound.

Another type of multiparticulate system which is also capable of achieving rapid drug dissolution is that of powders, granules, or pellets from water-soluble excipients which are coated with a compound provided herein so that the compound is located at the outer surface of the individual particles. In this type of system, the water-soluble low molecular weight excipient may be useful for preparing the cores of such coated particles, which can be subsequently coated with a coating composition comprising the compound and, for example, one or more additional excipients, such as a binder, a pore former, a saccharide, a sugar alcohol, a film-forming polymer, a plasticizer, or other excipients used in pharmaceutical coating compositions.

Also provided herein are kits. Typically, a kit includes one or more compounds or compositions as described herein. In certain embodiments, a kit can include one or more delivery systems, e.g., for delivering or administering a compound as provided herein, and directions for use of the kit (e.g., instructions for treating a patient). In another embodiment, the kit can include a compound or composition as described herein and a label that indicates that the contents are to be administered to a patient with cancer. In another embodiment, the kit can include a compound or composition as described herein and a label that indicates that the contents are to be administered to a patient with one or more of hepatocellular carcinoma, colon cancer, leukemia, lymphoma, sarcoma, ovarian cancer, diabetic retinopathy, pulmonary fibrosis, rheumatoid arthritis, sepsis, ankylosing spondylitis, psoriasis, scleroderma, mycotic and viral infections, bone and cartilage diseases, Alzheimer's disease, lung disease, bone/osteoporotic (wrist, spine, shoulder and hip) fractures, articular cartilage (chondral) defects, degenerative disc disease (or intervertebral disc degeneration), polyposis coli, bone density and vascular defects in the eye (Osteoporosis-pseudoglioma Syndrome, OPPG), familial exudative vitreoretinopathy, retinal angiogenesis, early coronary disease, tetra-amelia, Müllerian-duct regression and virilization, SERKAL syndrome, type II diabetes, Fuhrmann syndrome, Al-Awadi/Raas-Rothschild/Schinzel phocomelia syndrome, odonto-onycho-dermal dysplasia, obesity, split-hand/foot malformation, caudal duplication, tooth agenesis, Wilms tumor, skeletal dysplasia, focal dermal hypoplasia, autosomal recessive anonychia, neural tube defects, alpha-thalassemia (ATRX) syndrome, fragile X syndrome, ICF syndrome, Angelman syndrome, Prader-Willi syndrome, Beckwith-Wiedemann Syndrome, Norrie disease, and Rett syndrome.

Methods of Treatment

The compounds and compositions provided herein can be used as inhibitors and/or modulators of one or more components of the Wnt pathway, which may include one or more Wnt proteins, and thus can be used to treat a variety of disorders and diseases in which aberrant Wnt signaling is implicated, such as cancer and other diseases associated with abnormal angiogenesis, cellular proliferation, and cell cycling. Accordingly, the compounds and compositions provided herein can be used to treat cancer, to reduce or inhibit angiogenesis, to reduce or inhibit cellular proliferation, to correct a genetic disorder, and/or to treat a neurological condition/disorder/disease due to mutations or dysregulation of the Wnt pathway and/or of one or more of Wnt signaling components. Non-limiting examples of diseases which can be treated with the compounds and compositions provided herein include a variety of cancers, diabetic retinopathy, pulmonary fibrosis, rheumatoid arthritis, scleroderma, mycotic and viral infections, bone and cartilage diseases, neurological conditions/diseases such as Alzheimer's disease, amyotrophic lateral sclerosis (ALS), motor neuron disease, multiple sclerosis or autism, lung disease, bone/osteoporotic (wrist, spine, shoulder and hip) fractures, polyposis coli, bone density and vascular defects in the eye (Osteoporosis-pseudoglioma Syndrome, OPPG), familial exudative vitreoretinopathy, retinal angiogenesis, early coronary disease, tetra-amelia, Müllerian-duct regression and virilization, SERKAL syndrome, type II diabetes, Fuhrmann syndrome, Al-Awadi/Raas-Rothschild/Schinzel phocomelia syndrome, odonto-onycho-dermal dysplasia, obesity, split-hand/foot malformation, caudal duplication, tooth agenesis, Wilms tumor, skeletal dysplasia, focal dermal hypoplasia, autosomal recessive anonychia, neural tube defects, alpha-thalassemia (ATRX) syndrome, fragile X syndrome, ICF syndrome, Angelman syndrome, Prader-Willi syndrome, Beckwith-Wiedemann Syndrome, Norrie disease and Rett syndrome.

With respect to cancer, the Wnt pathway is known to be constitutively activated in a variety of cancers including, for example, colon cancer, hepatocellular carcinoma, lung cancer, ovarian cancer, prostate cancer, pancreatic cancer and leukemias such as CML, CLL and T-ALL. Accordingly, the compounds and compositions described herein may be used to treat these cancers in which the Wnt pathway is constitutively activated. In certain embodiments, the cancer is chosen from hepatocellular carcinoma, colon cancer, leukemia, lymphoma, sarcoma and ovarian cancer.

Other cancers can also be treated with the compounds and compositions described herein.

More particularly, cancers that may be treated by the compounds, compositions and methods described herein include, but are not limited to, the following:

1) Breast cancers, including, for example ER^+ breast cancer, ER^- breast cancer, $her2^-$ breast cancer, $her2^+$ breast cancer, stromal tumors such as fibroadenomas, phyllodes tumors, and sarcomas, and epithelial tumors such as large duct papillomas; carcinomas of the breast including in situ (noninvasive) carcinoma that includes ductal carcinoma in situ (including Paget's disease) and lobular carcinoma in situ, and invasive (infiltrating) carcinoma including, but not limited to, invasive ductal carcinoma, invasive lobular carcinoma, medullary carcinoma, colloid (mucinous) carcinoma, tubular carcinoma, and invasive papillary carcinoma; and miscellaneous malignant neoplasms. Further examples of breast cancers can include luminal A, luminal B, basal A, basal B, and triple negative breast cancer, which is estrogen receptor negative (ER^-), progesterone receptor negative, and her2 negative ($her2^-$). In some embodiments, the breast cancer may have a high risk Oncotype score.

2) Cardiac cancers, including, for example sarcoma, e.g., angiosarcoma, fibrosarcoma, rhabdomyosarcoma, and liposarcoma; myxoma; rhabdomyoma; fibroma; lipoma and teratoma.

3) Lung cancers, including, for example, bronchogenic carcinoma, e.g., squamous cell, undifferentiated small cell, undifferentiated large cell, and adenocarcinoma; alveolar and bronchiolar carcinoma; bronchial adenoma; sarcoma; lymphoma; chondromatous hamartoma; and mesothelioma.

4) Gastrointestinal cancer, including, for example, cancers of the esophagus, e.g., squamous cell carcinoma, adenocarcinoma, leiomyosarcoma, and lymphoma; cancers of the stomach, e.g., carcinoma, lymphoma, and leiomyosarcoma; cancers of the pancreas, e.g., ductal adenocarcinoma, insulinoma, glucagonoma, gastrinoma, carcinoid tumors, and vipoma; cancers of the small bowel, e.g., adenocarcinoma, lymphoma, carcinoid tumors, Kaposi's sarcoma, leiomyoma, hemangioma, lipoma, neurofibroma, and fibroma; cancers of the large bowel, e.g., adenocarcinoma, tubular adenoma, villous adenoma, hamartoma, and leiomyoma.

5) Genitourinary tract cancers, including, for example, cancers of the kidney, e.g., adenocarcinoma, Wilm's tumor (nephroblastoma), lymphoma, and leukemia; cancers of the bladder and urethra, e.g., squamous cell carcinoma, transitional cell carcinoma, and adenocarcinoma; cancers of the prostate, e.g., adenocarcinoma, and sarcoma; cancer of the testis, e.g., seminoma, teratoma, embryonal carcinoma, teratocarcinoma, choriocarcinoma, sarcoma, interstitial cell carcinoma, fibroma, fibroadenoma, adenomatoid tumors, and lipoma.

6) Liver cancers, including, for example, hepatoma, e.g., hepatocellular carcinoma; cholangiocarcinoma; hepatoblastoma; angiosarcoma; hepatocellular adenoma; and hemangioma.

7) Bone cancers, including, for example, osteogenic sarcoma (osteosarcoma), fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma (reticulum cell sarcoma), multiple myeloma, malignant giant cell tumor chordoma, osteochrondroma (osteocartilaginous exostoses), benign chondroma, chondroblastoma, chondromyxofibroma, osteoid osteoma and giant cell tumors.

8) Nervous system cancers, including, for example, cancers of the skull, e.g., osteoma, hemangioma, granuloma, xanthoma, and osteitis deformans; cancers of the meninges, e.g., meningioma, meningiosarcoma, and gliomatosis; cancers of the brain, e.g., astrocytoma, medulloblastoma, glioma, ependymoma, germinoma (pinealoma), glioblastoma multiform, oligodendroglioma, oligodendrocytoma, schwannoma, retinoblastoma, and congenital tumors; and cancers of the spinal cord, e.g., neurofibroma, meningioma, glioma, and sarcoma.

9) Gynecological cancers, including, for example, cancers of the uterus, e.g., endometrial carcinoma; cancers of the cervix, e.g., cervical carcinoma, and pre tumor cervical dysplasia; cancers of the ovaries, e.g., ovarian carcinoma, including serous cystadenocarcinoma, mucinous cystadenocarcinoma, unclassified carcinoma, granulosa theca cell tumors, Sertoli Leydig cell tumors, dysgerminoma, and malignant teratoma; cancers of the vulva, e.g., squamous cell carcinoma, intraepithelial carcinoma, adenocarcinoma, fibrosarcoma, and melanoma; cancers of the vagina, e.g., clear cell carcinoma, squamous cell carcinoma, botryoid sarcoma, and embryonal rhabdomyosarcoma; and cancers of the fallopian tubes, e.g., carcinoma.

10) Hematologic cancers, including, for example, cancers of the blood, e.g., acute myeloid leukemia, chronic myeloid leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, myeloproliferative diseases, multiple myeloma, and myelodysplastic syndrome, Hodgkin's lymphoma, non-Hodgkin's lymphoma (malignant lymphoma) and Waldenström's macroglobulinemia.

11) Skin cancers and skin disorders, including, for example, malignant melanoma and metastatic melanoma, basal cell carcinoma, squamous cell carcinoma, Kaposi's sarcoma, moles dysplastic nevi, lipoma, angioma, dermatofibroma, keloids, and scleroderma.

12) Adrenal gland cancers, including, for example, neuroblastoma.

More particularly, tumors of the central nervous system that may be treated by the compounds, compositions and methods described herein include:

1) Astrocytic tumors, e.g., diffuse astrocytoma (fibrillary, protoplasmic, gemistocytic, mixed), anaplastic (malignant) astrocytoma, glioblastoma multiforme (giant cell glioblastoma and gliosarcoma), pilocytic astrocytoma (pilomyxoid astrocytoma), pleomorphic xanthoastrocytoma, subependymal giant cell astrocytoma, and gliomatosis cerebri.

2) Oligodendroglial tumors, e.g., oligodendroglioma and anaplastic oligodendroglioma.

3) Oligoastrocytic tumors, e.g., oligoastrocytoma and anaplastic oligoastrocytoma.

4) Ependymal tumors, e.g., subependymoma, myxopapillary ependymoma, ependymoma, (cellular, papillary, clear cell, tanycytic), and anaplastic (malignant) ependymoma.

5) Choroid plexus tumors, e.g., choroid plexus papilloma, atypical choroid plexus papilloma, and choroid plexus carcinoma.

6) Neuronal and mixed neuronal-glial tumors, e.g., gangliocytoma, ganglioglioma, dysembryoplastic neuroepithelial tumor (DNET), dysplastic gangliocytoma of the cerebellum (Lhermitte-Duclos), desmoplastic infantile astrocytoma/ganglioglioma, central neurocytoma, anaplastic ganglioglioma, extraventricular neurocytoma, cerebellar liponeurocytoma, Papillary glioneuronal tumor, Rosette-forming glioneuronal tumor of the fourth ventricle, and paraganglioma of the filum terminale.

7) Pineal tumors, e.g., pineocytoma, pineoblastoma, papillary tumors of the pineal region, and pineal parenchymal tumor of intermediate differentiation.

8) Embryonal tumors, e.g., medulloblastoma (medulloblastoma with extensive nodularity, anaplastic medulloblastoma, desmoplastic, large cell, melanotic, medullomyoblastoma), medulloepithelioma, supratentorial primitive

neuroectodermal tumors, and primitive neuroectodermal tumors (PNETs) such as neuroblastoma, ganglioneuroblastoma, ependymoblastoma, and atypical teratoid/rhabdoid tumor.

9) Neuroblastic tumors, e.g., olfactory (esthesioneuroblastoma), olfactory neuroepithelioma, and neuroblastomas of the adrenal gland and sympathetic nervous system.

10) Glial tumors, e.g., astroblastoma, chordoid glioma of the third ventricle, and angiocentric glioma.

11) Tumors of cranial and paraspinal nerves, e.g., schwannoma, neurofibroma Perineurioma, and malignant peripheral nerve sheath tumor.

12) Tumors of the meninges such as tumors of meningothelial cells, e.g., meningioma (atypical meningioma and anaplastic meningioma); mesenchymal tumors, e.g., lipoma, angiolipoma, hibernoma, liposarcoma, solitary fibrous tumor, fibrosarcoma, malignant fibrous histiocytoma, leiomyoma, leiomyosarcoma, rhabdomyoma, rhabdomyosarcoma, chondroma, chondrosarcoma, osteoma, osteosarcoma, osteochondroma, haemangioma, epithelioid hemangioendothelioma, haemangiopericytoma, anaplastic haemangiopericytoma, angiosarcoma, Kaposi Sarcoma, and Ewing Sarcoma; primary melanocytic lesions, e.g., diffuse melanocytosis, melanocytoma, malignant melanoma, meningeal melanomatosis; and hemangioblastomas.

13) Tumors of the hematopoietic system, e.g., malignant Lymphomas, plasmocytoma, and granulocytic sarcoma.

14) Germ cell tumors, e.g., germinoma, embryonal carcinoma, yolk sac tumor, choriocarcinoma, teratoma, and mixed germ cell tumors.

15) Tumors of the sellar region, e.g., craniopharyngioma, granular cell tumor, pituicytoma, and spindle cell oncocytoma of the adenohypophysis.

Cancers may be solid tumors that may or may not be metastatic. Cancers may also occur, as in leukemia, as a diffuse tissue. Thus, the term "tumor cell," as provided herein, includes a cell afflicted by any one of the above identified disorders.

A method of treating cancer using a compound or composition as described herein may be combined with existing methods of treating cancers, for example by chemotherapy, irradiation, or surgery (e.g., oophorectomy). In some embodiments, a compound or composition can be administered before, during, or after another anticancer agent or treatment.

The compounds and compositions described herein can be used as anti-angiogenesis agents and as agents for modulating and/or inhibiting the activity of protein kinases, thus providing treatments for cancer and other diseases associated with cellular proliferation mediated by protein kinases. For example, the compounds described herein can inhibit the activity of one or more kinases. Accordingly, provided herein is a method of treating cancer or preventing or reducing angiogenesis through kinase inhibition.

In addition, and including treatment of cancer, the compounds and compositions described herein can function as cell-cycle control agents for treating proliferative disorders in a patient. Disorders associated with excessive proliferation include, for example, cancers, scleroderma, immunological disorders involving undesired proliferation of leukocytes, and restenosis and other smooth muscle disorders. Furthermore, such compounds may be used to prevent de-differentiation of post-mitotic tissue and/or cells.

Diseases or disorders associated with uncontrolled or abnormal cellular proliferation include, but are not limited to, the following:

a variety of cancers, including, but not limited to, carcinoma, hematopoietic tumors of lymphoid lineage, hematopoietic tumors of myeloid lineage, tumors of mesenchymal origin, tumors of the central and peripheral nervous system and other tumors including melanoma, seminoma and Kaposi's sarcoma.

a disease process which features abnormal cellular proliferation, e.g., benign prostatic hyperplasia, familial adenomatosis polyposis, neurofibromatosis, atherosclerosis, arthritis, glomerulonephritis, restenosis following angioplasty or vascular surgery, inflammatory bowel disease, transplantation rejection, endotoxic shock, and fungal infections. Fibrotic disorders such as skin fibrosis; scleroderma; progressive systemic fibrosis; lung fibrosis; muscle fibrosis; kidney fibrosis; glomerulosclerosis; glomerulonephritis; hypertrophic scar formation; uterine fibrosis; renal fibrosis; cirrhosis of the liver, liver fibrosis; fatty liver disease (FLD); adhesions, such as those occurring in the abdomen, pelvis, spine or tendons; chronic obstructive pulmonary disease; fibrosis following myocardial infarction; pulmonary fibrosis; fibrosis and scarring associated with diffuse/interstitial lung disease; central nervous system fibrosis, such as fibrosis following stroke; fibrosis associated with neuro-degenerative disorders such as Alzheimer's Disease or multiple sclerosis; fibrosis associated with proliferative vitreoretinopathy (PVR); restenosis; endometriosis; ischemic disease and radiation fibrosis.

defective apoptosis-associated conditions, such as cancers (including but not limited to those types mentioned herein), viral infections (including but not limited to herpesvirus, poxvirus, Epstein-Barr virus, Sindbis virus and adenovirus), prevention of AIDS development in HIV-infected individuals, autoimmune diseases (including but not limited to systemic lupus erythematosus, rheumatoid arthritis, sepsis, ankylosing spondylitis, psoriasis, scleroderma, autoimmune mediated glomerulonephritis, inflammatory bowel disease and autoimmune diabetes mellitus), neuro-degenerative disorders (including but not limited to Alzheimer's disease, lung disease, amyotrophic lateral sclerosis, retinitis pigmentosa, Parkinson's disease, AIDS-related dementia, spinal muscular atrophy and cerebellar degeneration), myelodysplastic syndromes, aplastic anemia, ischemic injury associated with myocardial infarctions, stroke and reperfusion injury, arrhythmia, atherosclerosis, toxin-induced or alcohol related liver diseases, hematological diseases (including but not limited to chronic anemia and aplastic anemia), degenerative diseases of the musculoskeletal system (including but not limited to osteoporosis and arthritis), tendinopathies such as tendinitis and tendinosis, aspirin-sensitive rhinosinusitis, cystic fibrosis, multiple sclerosis, kidney diseases and cancer pain.

genetic diseases due to mutations in Wnt signaling components, such as polyposis coli, bone density and vascular defects in the eye (Osteoporosis-pseudoglioma Syndrome, OPPG), familial exudative vitreoretinopathy, retinal angiogenesis, early coronary disease, tetra-amelia, Müllerian-duct regression and virilization, SERKAL syndrome, type II diabetes, Fuhrmann syndrome, Al-Awadi/Raas-Rothschild/Schinzel phocomelia syndrome, odonto-onycho-dermal dysplasia, obesity, split-hand/foot malformation, caudal duplication, tooth agenesis, Wilms tumor, skeletal dysplasia, focal dermal hypoplasia, autosomal

recessive anonychia, neural tube defects, alpha-thalassemia (ATRX) syndrome, fragile X syndrome, ICF syndrome, Angelman syndrome, Prader-Willi syndrome, Beckwith-Wiedemann Syndrome, Norrie disease and Rett syndrome.

The compounds and compositions provided herein have been found to possess immunomodulatory activities and are expected to control the innate and adaptive immune system (e.g. macrophages, microglia, dendritic cells, B and T cells) and suppress pro-inflammatory cytokine release (e.g. TNF, IL-6, IL-1, IFNγ) which is well known to be involved in chronic inflammation in a wide variety of disease areas. Therefore compounds and compositions provided herein can used to treat chronic inflammation associated with disorders and diseases including but not limited to eye disorders, joint pain, arthritis (rheumatoid, osteo, psoriatic gout), cancers (colon, breast, lung, pancreas, and others), gastrointestinal disorders (ulcerative colitis and inflammatory bowel diseases), pulmonary disorders (chronic obstructive pulmonary disorder and asthma), allergies, skin disorders (atopic dermatitis and psoriasis), diabetes, pancreatitis, tendonitis, hepatitis, heart disease, myocarditis, stroke, lupus, and neurological disorders such as multiple sclerosis, Parkinson's and dementia including Alzheimer's disease.

The compounds and compositions provided herein can be used as inhibitors and/or modulators of the enzyme DYRK1A, and thus can be used to treat a variety of disorders and diseases associated with tau protein, amyloid, alpha-synuclein, TDP-43 or FUS pathology including, but not limited to, Alzheimer's disease, amyotrophic lateral sclerosis (ALS), down syndrome, frontotemporal dementia (FTD) including FTD with Parkinsonism-17 (FTDP-17), behavioural variant frontotemporal dementia (bvFTD), FTD in patients with motor neuron disease (MND) (typically amyotrophic lateral sclerosis, also called FTD-ALS), corticobasal degeneration (CBD) (also called corticobasal ganglionic degeneration), progressive supranuclear palsy, primary progressive aphasia (PPA), globular glial tauopathy (GGT), myotonic dystrophy type 1 (DM1) (also called Steinert disease), myotonic dystrophy type 2 (DM2) (also called proximal myotonic myopathy), Guam complex, argyrophilic grain disease, dementia pugilistica, post-encephalitic parkinsonism, Lewy body dementia, Parkinson's disease, Pick's disease, and additional diseases with pronounced neurodegeneration such as autism, dementia, epilepsy, Huntington's disease, multiple sclerosis; diseases and disorders associated with acquired brain injury such as chronic traumatic encephalopathy, traumatic brain injury, tumor, and stroke.

Non-limiting examples of neurological disorders (e.g., neurological conditions and neurological diseases) which can be treated with the compounds and compositions provided herein include Alzheimer's disease, aphasia, apraxia, arachnoiditis, ataxia telangiectasia, attention deficit hyperactivity disorder, auditory processing disorder, autism, alcoholism, Bell's palsy, bipolar disorder, brachial plexus injury, Canavan disease, carpal tunnel syndrome, causalgia, central pain syndrome, central pontine myelinolysis, centronuclear myopathy, cephalic disorder, cerebral aneurysm, cerebral arteriosclerosis, cerebral atrophy, cerebral gigantism, cerebral palsy, cerebral vasculitis, cervical spinal stenosis, Charcot-Marie-Tooth disease, Chiari malformation, chronic fatigue syndrome, chronic inflammatory demyelinating polyneuropathy (CIDP), chronic pain, Coffin-Lowry syndrome, complex regional pain syndrome, compression neuropathy, congenital facial diplegia, corticobasal degeneration, cranial arteritis, craniosynostosis, Creutzfeldt-Jakob disease, cumulative trauma disorder, Cushing's syndrome, cytomegalic inclusion body disease (CIBD), Dandy-Walker syndrome, Dawson disease, De Morsier's syndrome, Dejerine-Klumpke palsy, Dejerine-Sottas disease, delayed sleep phase syndrome, dementia, dermatomyositis, developmental dyspraxia, diabetic neuropathy, diffuse sclerosis, Dravet syndrome, dysautonomia, dyscalculia, dysgraphia, dyslexia, dystonia, empty sella syndrome, encephalitis, encephalocele, encephalotrigeminal angiomatosis, encopresis, epilepsy, Erb's palsy, erythromelalgia, essential tremor, Fabry's disease, Fahr's syndrome, familial spastic paralysis, febrile seizure, Fisher syndrome, Friedreich's ataxia, fibromyalgia, Foville's syndrome, Gaucher's disease, Gerstmann's syndrome, giant cell arteritis, giant cell inclusion disease, globoid cell leukodystrophy, gray matter heterotopia, Guillain-Barré syndrome, HTLV-1 associated myelopathy, Hallervorden-Spatz disease, hemifacial spasm, hereditary spastic paraplegia, heredopathia atactica polyneuritiformis, herpes zoster oticus, herpes zoster, Hirayama syndrome, holoprosencephaly, Huntington's disease, hydranencephaly, hydrocephalus, hypercortisolism, hypoxia, immune-mediated encephalomyelitis, inclusion body myositis, incontinentia pigmenti, infantile phytanic acid storage disease, infantile Refsum disease, infantile spasms, inflammatory myopathy, intracranial cyst, intracranial hypertension, Joubert syndrome, Karak syndrome, Kearns-Sayre syndrome, Kennedy disease, Kinsbourne syndrome, Klippel Feil syndrome, Krabbe disease, Kugelberg-Welander disease, kuru, Lafora disease, Lambert-Eaton myasthenic syndrome, Landau-Kleffner syndrome, lateral medullary (Wallenberg) syndrome, Leigh's disease, Lennox-Gastaut syndrome, Lesch-Nyhan syndrome, leukodystrophy, Lewy body dementia, lissencephaly, locked-in syndrome, Lou Gehrig's disease, lumbar disc disease, lumbar spinal stenosis, Lyme disease, Machado-Joseph disease (Spinocerebellar ataxia type 3), macrencephaly, macropsia, megalencephaly, Melkersson-Rosenthal syndrome, Meniere's disease, meningitis, Menkes disease, metachromatic leukodystrophy, microcephaly, micropsia, Miller Fisher syndrome, misophonia, mitochondrial myopathy, Mobius syndrome, monomelic amyotrophy, motor neuron disease, motor skills disorder, Moyamoya disease, mucopolysaccharidoses, multi-infarct dementia, multifocal motor neuropathy, multiple sclerosis, multiple system atrophy, muscular dystrophy, myalgic encephalomyelitis, myasthenia gravis, myelinoclastic diffuse sclerosis, myoclonic Encephalopathy of infants, myoclonus, myopathy, myotubular myopathy, myotonia congenital, narcolepsy, neurofibromatosis, neuroleptic malignant syndrome, lupus erythematosus, neuromyotonia, neuronal ceroid lipofuscinosis, Niemann-Pick disease, O'Sullivan-McLeod syndrome, occipital Neuralgia, occult Spinal Dysraphism Sequence, Ohtahara syndrome, olivopontocerebellar atrophy, opsoclonus myoclonus syndrome, optic neuritis, orthostatic hypotension, palinopsia, paresthesia, Parkinson's disease, paramyotonia Congenita, paraneoplastic diseases, paroxysmal attacks, Parry-Romberg syndrome, Pelizaeus-Merzbacher disease, periodic paralyses, peripheral neuropathy, photic sneeze reflex, phytanic acid storage disease, Pick's disease, polymicrogyria (PMG), polymyositis, porencephaly, post-polio syndrome, postherpetic neuralgia (PHN), postural hypotension, Prader-Willi syndrome, primary lateral sclerosis, prion diseases, progressive hemifacial atrophy, progressive multifocal leukoencephalopathy, progressive supranuclear palsy, pseudotumor cerebri, Ramsay Hunt syndrome type I, Ramsay Hunt syndrome type II, Ramsay Hunt syndrome type III, Rasmussen's encephalitis, reflex neurovascular dystrophy, Refsum disease, restless

legs syndrome, retrovirus-associated myelopathy, Rett syndrome, Reye's syndrome, rhythmic movement disorder, Romberg syndrome, Saint Vitus dance, Sandhoff disease, schizophrenia, Schilder's disease, schizencephaly, sensory integration dysfunction, septo-optic dysplasia, Shy-Drager syndrome, Sjögren's syndrome, snatiation, Sotos syndrome, spasticity, spina bifida, spinal cord tumors, spinal muscular atrophy, spinocerebellar ataxia, Steele-Richardson-Olszewski syndrome, Stiff-person syndrome, stroke, Sturge-Weber syndrome, subacute sclerosing panencephalitis, subcortical arteriosclerotic encephalopathy, superficial siderosis, Sydenham's chorea, syncope, synesthesia, syringomyelia, tarsal tunnel syndrome, tardive dyskinesia, tardive dysphrenia, Tarlov cyst, Tay-Sachs disease, temporal arteritis, tetanus, tethered spinal cord syndrome, Thomsen disease, thoracic outlet syndrome, tic douloureux, Todd's paralysis, Tourette syndrome, toxic encephalopathy, transient ischemic attack, transmissible spongiform encephalopathies, transverse myelitis, tremor, trigeminal neuralgia, tropical spastic paraparesis, trypanosomiasis, tuberous sclerosis, ubisiosis, Von Hippel-Lindau disease (VHL), Viliuisk Encephalomyelitis (VE), Wallenberg's syndrome, Werdnig, Hoffman disease, west syndrome, Williams syndrome, Wilson's disease, and Zellweger syndrome.

The compounds and compositions may also be useful in the inhibition of the development of invasive cancer, tumor angiogenesis and metastasis.

In some embodiments, the disclosure provides a method for treating a disease or disorder associated with aberrant cellular proliferation by administering to a patient in need of such treatment an effective amount of one or more of the compounds of Formula (I), in combination (simultaneously or sequentially) with at least one other agent.

In some embodiments, the disclosure provides a method of treating or ameliorating in a patient a disorder or disease selected from the group consisting of: cancer, pulmonary fibrosis, idiopathic pulmonary fibrosis (IPF), degenerative disc disease, bone/osteoporotic fractures, bone or cartilage disease, and osteoarthritis, the method comprising administering to the patient a therapeutically effective amount of a compound according to claim **1**, or a pharmaceutically acceptable salt thereof.

In some embodiments, the pharmaceutical composition comprises a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

In some embodiments, the method of treats a disorder or disease in which aberrant Wnt signaling is implicated in a patient, the method comprises administering to the patient a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In some embodiments, the disorder or disease is the pain and inflammation associated with cancer.

In some embodiments, the disorder or disease is the pain and inflammation associated with a joint.

In some embodiments, the disorder or disease is the pain and inflammation associated with the knee.

In some embodiments, the disorder or disease is the pain and inflammation associated with the hip.

In some embodiments, the disorder or disease is the pain and inflammation associated with the shoulder.

In some embodiments, the disorder or disease is the pain and inflammation associated with arthritis.

In some embodiments, the disorder or disease is the pain and inflammation associated with gastrointestinal disorders.

In some embodiments, the disorder or disease is the pain and inflammation associated with pulmonary disorders.

In some embodiments, the disorder or disease is the pain and inflammation associated with allergies.

In some embodiments, the disorder or disease is the pain and inflammation associated with skin disorders.

In some embodiments, the disorder or disease is the pain and inflammation associated with diabetes.

In some embodiments, the disorder or disease is the pain and inflammation associated with pancreatitis.

In some embodiments, the disorder or disease is the pain and inflammation associated with tendonitis.

In some embodiments, the disorder or disease is the pain and inflammation associated with heart disease.

In some embodiments, the disorder or disease is the pain and inflammation associated with lupus.

In some embodiments, the disorder or disease is the pain and inflammation associated with a neurological disorder.

In some embodiments, the disorder or disease is the pain and inflammation associated with multiple sclerosis.

In some embodiments, the disorder or disease is the pain and inflammation associated with Parkinson's.

In some embodiments, the disorder or disease is cancer.

In some embodiments, the disorder or disease is systemic inflammation.

In some embodiments, the disorder or disease is metastatic melanoma.

In some embodiments, the disorder or disease is fatty liver disease.

In some embodiments, the disorder or disease is liver fibrosis.

In some embodiments, the disorder or disease is tendon regeneration.

In some embodiments, the disorder or disease is diabetes.

In some embodiments, the disorder or disease is degenerative disc disease.

In some embodiments, the disorder or disease is osteoarthritis.

In some embodiments, the disorder or disease is diabetic retinopathy.

In some embodiments, the disorder or disease is pulmonary fibrosis.

In some embodiments, the disorder or disease is idiopathic pulmonary fibrosis (IPF).

In some embodiments, the disorder or disease is degenerative disc disease.

In some embodiments, the disorder or disease is rheumatoid arthritis.

In some embodiments, the disorder or disease is scleroderma.

In some embodiments, the disorder or disease is a mycotic or viral infection.

In some embodiments, the disorder or disease is a bone or cartilage disease.

In some embodiments, the disorder or disease is a neurological disorder.

In some embodiments, the disorder or disease is Alzheimer's disease.

In some embodiments, the disorder or disease is osteoarthritis.

In some embodiments, the disorder or disease is lung disease.

In some embodiments, the disorder or disease is a genetic disease caused by mutations in Wnt signaling components, wherein the genetic disease is selected from: polyposis coli, osteoporosis-pseudoglioma syndrome, familial exudative vitreoretinopathy, retinal angiogenesis, early coronary disease, tetra-amelia syndrome, Mëllerian-duct regression and virilization, SERKAL syndrome, diabetes mellitus type 2,

Fuhrmann syndrome, Al-Awadi/Raas-Rothschild/Schinzel phocomelia syndrome, odonto-onycho-dermal dysplasia, obesity, split-hand/foot malformation, caudal duplication syndrome, tooth agenesis, Wilms tumor, skeletal dysplasia, focal dermal hypoplasia, autosomal recessive anonychia, neural tube defects, alpha-thalassemia (ATRX) syndrome, fragile X syndrome, ICF syndrome, Angelman syndrome, Prader-Willi syndrome, Beckwith-Wiedemann Syndrome, Norrie disease and Rett syndrome.

In some embodiments, the patient is a human.

In some embodiments, the cancer is chosen from: hepatocellular carcinoma, colon cancer, breast cancer, pancreatic cancer, chronic myeloid leukemia (CML), chronic myelomonocytic leukemia, chronic lymphocytic leukemia (CLL), acute myeloid leukemia, acute lymphocytic leukemia, Hodgkin lymphoma, lymphoma, sarcoma and ovarian cancer.

In some embodiments, the cancer is chosen from: lung cancer—non-small cell, lung cancer—small cell, multiple myeloma, nasopharyngeal cancer, neuroblastoma, osteosarcoma, penile cancer, pituitary tumors, prostate cancer, retinoblastoma, rhabdomyosarcoma, salivary gland cancer, skin cancer—basal and squamous cell, skin cancer—melanoma, small intestine cancer, stomach (gastric) cancers, testicular cancer, thymus cancer, thyroid cancer, uterine sarcoma, vaginal cancer, vulvar cancer, laryngeal or hypopharyngeal cancer, kidney cancer, Kaposi sarcoma, gestational trophoblastic disease, gastrointestinal stromal tumor, gastrointestinal carcinoid tumor, gallbladder cancer, eye cancer (melanoma and lymphoma), Ewing tumor, esophagus cancer, endometrial cancer, colorectal cancer, cervical cancer, brain or spinal cord tumor, bone metastasis, bone cancer, bladder cancer, bile duct cancer, anal cancer and adrenal cortical cancer.

In some embodiments, the cancer is hepatocellular carcinoma.

In some embodiments, the cancer is colon cancer.

In some embodiments, the cancer is colorectal cancer.

In some embodiments, the cancer is breast cancer.

In some embodiments, the cancer is pancreatic cancer.

In some embodiments, the cancer is chronic myeloid leukemia (CML).

In some embodiments, the cancer is chronic myelomonocytic leukemia.

In some embodiments, the cancer is chronic lymphocytic leukemia (CLL).

In some embodiments, the cancer is acute myeloid leukemia.

In some embodiments, the cancer is acute lymphocytic leukemia.

In some embodiments, the cancer is Hodgkin lymphoma.

In some embodiments, the cancer is lymphoma.

In some embodiments, the cancer is sarcoma.

In some embodiments, the cancer is ovarian cancer.

In some embodiments, the cancer is lung cancer—non-small cell.

In some embodiments, the cancer is lung cancer—small cell.

In some embodiments, the cancer is multiple myeloma.

In some embodiments, the cancer is nasopharyngeal cancer.

In some embodiments, the cancer is neuroblastoma.

In some embodiments, the cancer is osteosarcoma.

In some embodiments, the cancer is penile cancer.

In some embodiments, the cancer is pituitary tumors.

In some embodiments, the cancer is prostate cancer.

In some embodiments, the cancer is retinoblastoma.

In some embodiments, the cancer is rhabdomyosarcoma.

In some embodiments, the cancer is salivary gland cancer.

In some embodiments, the cancer is skin cancer—basal and squamous cell.

In some embodiments, the cancer is skin cancer—melanoma.

In some embodiments, the cancer is small intestine cancer.

In some embodiments, the cancer is stomach (gastric) cancers.

In some embodiments, the cancer is testicular cancer.

In some embodiments, the cancer is thymus cancer.

In some embodiments, the cancer is thyroid cancer.

In some embodiments, the cancer is uterine sarcoma.

In some embodiments, the cancer is vaginal cancer.

In some embodiments, the cancer is vulvar cancer.

In some embodiments, the cancer is Wilms tumor.

In some embodiments, the cancer is laryngeal or hypopharyngeal cancer.

In some embodiments, the cancer is kidney cancer.

In some embodiments, the cancer is Kaposi sarcoma.

In some embodiments, the cancer is gestational trophoblastic disease.

In some embodiments, the cancer is gastrointestinal stromal tumor.

In some embodiments, the cancer is gastrointestinal carcinoid tumor.

In some embodiments, the cancer is gallbladder cancer.

In some embodiments, the cancer is eye cancer (melanoma and lymphoma).

In some embodiments, the cancer is Ewing tumor.

In some embodiments, the cancer is esophagus cancer.

In some embodiments, the cancer is endometrial cancer.

In some embodiments, the cancer is colorectal cancer.

In some embodiments, the cancer is cervical cancer.

In some embodiments, the cancer is brain or spinal cord tumor.

In some embodiments, the cancer is bone metastasis.

In some embodiments, the cancer is bone cancer.

In some embodiments, the cancer is bladder cancer.

In some embodiments, the cancer is bile duct cancer.

In some embodiments, the cancer is anal cancer.

In some embodiments, the cancer is adrenal cortical cancer.

In some embodiments, the disorder or disease is a neurological condition, disorder or disease, wherein the neurological condition/disorder/disease is selected from: Alzheimer's disease, frontotemporal dementias, dementia with Lewy bodies, prion diseases, Parkinson's disease, Huntington's disease, progressive supranuclear palsy, corticobasal degeneration, multiple system atrophy, amyotrophic lateral sclerosis (ALS), inclusion body myositis, autism, degenerative myopathies, diabetic neuropathy, other metabolic neuropathies, endocrine neuropathies, orthostatic hypotension, multiple sclerosis and Charcot-Marie-Tooth disease.

In some embodiments, the disorder or disease is a neurological disease or disorder associated with tau protein, amyloid, alpha-synuclein pathology, Tar DNA-binding Protein of 43 KDa (TDP-43), Prion protein PrP or fused in sarcoma (FUS).

In some embodiments, the disorder or disease is selected from the group consisting of: Alzheimer's Disease, Amyotrophic Lateral Sclerosis, Down Syndrome, Frontotemporal Dementia with Parkinsonism-17 (FTDP-17), Lewy body dementia, Parkinson's Disease, Pick's Disease, and additional diseases with pronounced neurodegeneration such as

Autism, Dementia, Epilepsy, Huntington's Disease, Multiple Sclerosis; diseases and disorders associated with acquired brain injury such as Chronic Traumatic Encephalopathy, Traumatic Brain Injury, Tumor, and Stroke.

In some embodiments, a compound of Formula (I) inhibits DYRK1A.

In some embodiments, a compound of Formula (I) inhibits GSK3.

In some embodiments, a compound of Formula (I) inhibits GSK3β.

In some embodiments, a compound of Formula (I) inhibits DYRK1A and GSK3β.

In some embodiments, the compound of Formula (I) inhibits one or more proteins in the Wnt pathway.

In some embodiments, the compound of Formula (I) inhibits signaling induced by one or more Wnt proteins.

In some embodiments, the Wnt proteins are chosen from: WNT1, WNT2, WNT2B, WNT3, WNT3A, WNT4, WNT5A, WNT5B, WNT6, WNT7A, WNT7B, WNT8A, WNT8B, WNT9A, WNT9B, WNT10A, WNT10B, WNT11, and WNT16.

In some embodiments, the compound of Formula (I) inhibits a kinase activity.

In some embodiments, the method treats a disease or disorder mediated by the Wnt pathway in a patient, the method comprises administering to the patient a therapeutically effective amount of a compound (or compounds) of Formula (I), or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of Formula (I) inhibits one or more Wnt proteins.

In some embodiments, the method treats a disease or disorder mediated by kinase activity in a patient, the method comprises administering to the patient a therapeutically effective amount of a compound (or compounds) of Formula (I), or a pharmaceutically acceptable salt thereof.

In some embodiments, the disease or disorder comprises tumor growth, cell proliferation, or angiogenesis.

In some embodiments, the method inhibits the activity of a protein kinase receptor, the method comprises contacting the receptor with an effective amount of a compound (or compounds) of Formula (I), or a pharmaceutically acceptable salt thereof.

In some embodiments, the method treats a disease or disorder associated with aberrant cellular proliferation in a patient; the method comprises administering to the patient a therapeutically effective amount of a compound (or compounds) of Formula (I), or a pharmaceutically acceptable salt thereof.

In some embodiments, the method prevents or reduces angiogenesis in a patient; the method comprises administering to the patient a therapeutically effective amount of a compound (or compounds) of Formula (I), or a pharmaceutically acceptable salt thereof.

In some embodiments, the method prevents or reduces abnormal cellular proliferation in a patient; the method comprises administering to the patient a therapeutically effective amount of a compound (or compounds) of Formula (I), or a pharmaceutically acceptable salt thereof.

In some embodiments, the method treats a disease or disorder associated with aberrant cellular proliferation in a patient, the method comprises administering to the patient a pharmaceutical composition comprising one or more of the compounds of claim **1** in combination with a pharmaceutically acceptable carrier and one or more other agents.

Moreover, the compounds and compositions, for example, as inhibitors of the cyclin-dependent kinases (CDKs), can modulate the level of cellular RNA and DNA synthesis and therefore are expected to be useful in the treatment of viral infections such as HIV, human papilloma virus, herpes virus, Epstein-Barr virus, adenovirus, Sindbis virus, pox virus and the like.

Compounds and compositions described herein can inhibit the kinase activity of, for example, CDK/cyclin complexes, such as those active in the G_0 or G_1 stage of the cell cycle, e.g., CDK2, CDK4, and/or CDK6 complexes.

Evaluation of Biological Activity

The biological activity of the compounds described herein can be tested using any suitable assay known to those of skill in the art, see, e.g., WO 2001/053268 and WO 2005/009997. For example, the activity of a compound may be tested using one or more of the test methods outlined below.

In one example, tumor cells may be screened for Wnt independent growth. In such a method, tumor cells of interest are contacted with a compound (i.e. inhibitor) of interest, and the proliferation of the cells, e.g. by uptake of tritiated thymidine, is monitored. In some embodiments, tumor cells may be isolated from a candidate patient who has been screened for the presence of a cancer that is associated with a mutation in the Wnt signaling pathway. Candidate cancers include, without limitation, those listed above.

In another example, one may utilize in vitro assays for Wnt biological activity, e.g. stabilization of β-catenin and promoting growth of stem cells. Assays for biological activity of Wnt include stabilization of β-catenin, which can be measured, for example, by serial dilutions of a candidate inhibitor composition. An exemplary assay for Wnt biological activity contacts a candidate inhibitor with cells containing constitutively active Wnt/β-catenin signaling. The cells are cultured for a period of time sufficient to stabilize β-catenin, usually at least about 1 hour, and lysed. The cell lysate is resolved by SDS PAGE, then transferred to nitrocellulose and probed with antibodies specific for β-catenin.

In a further example, the activity of a candidate compound can be measured in a Xenopus secondary axis bioassay (Leyns, L. et al. *Cell* (1997), 88(6), 747-756).

In another example, in vitro assays for DYRK1A biological activity may be used, e.g. regulation of microtubule-associated protein tau (MAPT/Tau) phosphorylation in neuronal cell line such as the human SH-SY5Y neuroblastoma cell line. Assays for DYRK1A-regulated level of phosphorylation can include monitoring levels of basal pSer396 Tau, which can be measured, for example, by serial dilutions of a candidate inhibitor composition using a ten micromolar top concentration and detected by ELISA or Western Blotting. An exemplary assay for DYRK-1A-regulated phosphorylation uses the SH-SY5Y cells cultured in a 96 well plate format for a period of time sufficient to stabilize microtubules and Tau phosphorylation, usually at least 2 days, then treated with a ⅓ serial dilution of compounds overnight and lysed. The cell lysate is resolved by SDS PAGE, then transferred to nitrocellulose and probed with an antibody specific for pSer396 Tau. The chemiluminescence signal for HRP-linked antibodies used in western blotting is detected using a Carestream Image Station and blot densitometry for pSer396 and beta-actin are analyzed using ImageJ (NIH).

In a further example, the activity of a candidate compound can be measured by ELISA by adding the lysate mentioned above onto total Tau-coated plates and detected with a specific pSer396 antibody. Colorimetric detection of ELISA signal is performed by Cytation3 plate reader (Biotek).

To further illustrate this disclosure, the following examples are included. The examples should not, of course, be construed as specifically limiting the disclosure. Variations of these examples within the scope of the claims are

within the purview of one skilled in the art and are considered to fall within the scope of the disclosure as described, and claimed herein. The reader will recognize that the skilled artisan, armed with the present disclosure, and skill in the art is able to prepare and use the disclosure without exhaustive examples.

EXAMPLES

Compound Preparation

The starting materials used in preparing the compounds of the disclosure are known, made by known methods, or are commercially available. It will be apparent to the skilled artisan that methods for preparing precursors and functionality related to the compounds claimed herein are generally described in the literature. The skilled artisan given the literature and this disclosure is well equipped to prepare any of the compounds.

It is recognized that the skilled artisan in the art of organic chemistry can readily carry out manipulations without further direction, that is, it is well within the scope and practice of the skilled artisan to carry out these manipulations. These include reduction of carbonyl compounds to their corresponding alcohols, oxidations, acylations, aromatic substitutions, both electrophilic and nucleophilic, etherifications, esterification and saponification and the like. These manipulations are discussed in standard texts such as *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure* 7th Ed., John Wiley & Sons (2013), Carey and Sundberg, *Advanced Organic Chemistry* 5th Ed., Springer (2007), *Comprehensive Organic Transformations: A Guide to Functional Group Transformations,* 2nd Ed., John Wiley & Sons (1999) (incorporated herein by reference in its entirety) and the like.

The skilled artisan will readily appreciate that certain reactions are best carried out when other functionality is masked or protected in the molecule, thus avoiding any undesirable side reactions and/or increasing the yield of the reaction. Often the skilled artisan utilizes protecting groups to accomplish such increased yields or to avoid the undesired reactions. These reactions are found in the literature and are also well within the scope of the skilled artisan. Examples of many of these manipulations can be found for example in P. Wuts *Greene's Protective Groups in Organic Synthesis,* 5th Ed., John Wiley & Sons (2014), incorporated herein by reference in its entirety.

Trademarks used herein are examples only and reflect illustrative materials used at the time of the disclosure. The skilled artisan will recognize that variations in lot, manufacturing processes, and the like, are expected. Hence the examples, and the trademarks used in them are non-limiting, and they are not intended to be limiting, but are merely an illustration of how a skilled artisan may choose to perform one or more of the embodiments of the disclosure.

(^{1}H) nuclear magnetic resonance spectra (NMR) were measured in the indicated solvents on a Bruker NMR spectrometer (Avance™ DRX300, 300 MHz for ^{1}H or Avance™ DRX500, 500 MHz for ^{1}H) or Varian NMR spectrometer (Mercury 400BB, 400 MHz for ^{1}H). Peak positions are expressed in parts per million (ppm) downfield from tetramethylsilane. The peak multiplicities are denoted as follows, s, singlet; d, doublet; t, triplet; q, quartet; ABq, AB quartet; quin, quintet; sex, sextet; sep, septet; non, nonet; dd, doublet of doublets; ddd, doublet of doublets of doublets; d/ABq, doublet of AB quartet; dt, doublet of triplets; td, triplet of doublets; dq, doublet of quartets; m, multiplet.

The following abbreviations have the indicated meanings:

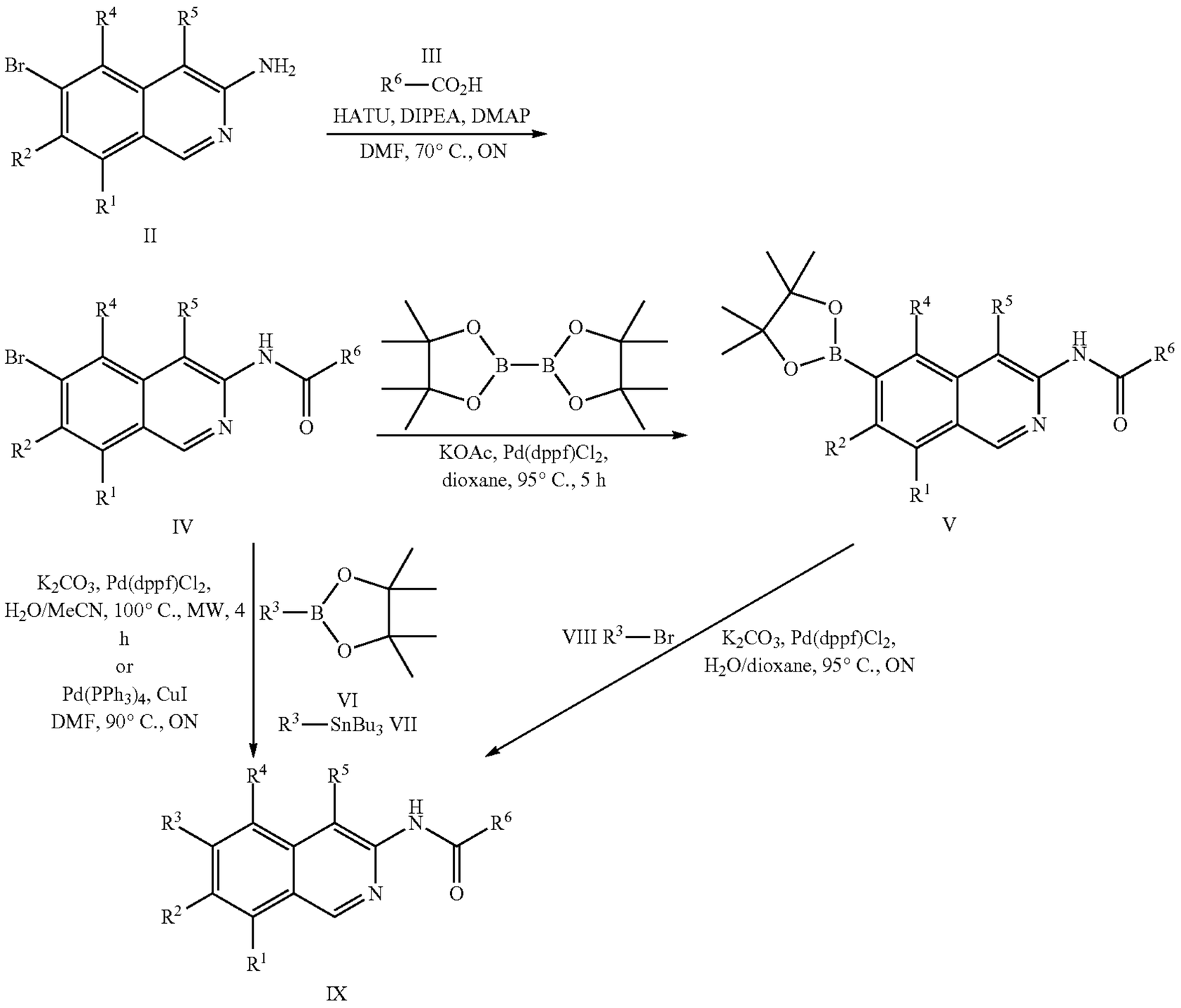
brine=saturated aqueous sodium chloride
$CDCl_3$=deuterated chloroform
DCE=dichloroethane
DCM=dichloromethane
DIPEA=N,N-diisopropylethylamine
DMAP=4-dimethylaminopyridine
DMF=N,N-dimethylformamide
DMSO-d_6=deuterated dimethylsulfoxide
ESIMS=electron spray mass spectrometry
EtOAc=ethyl acetate
HATU=1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate
HCl=hydrochloric acid
HOAc=acetic acid
ISCO=Teledyne ISCO, Inc brand CombiFlash® Rf 200
KOAc=potassium acetate
LAH=Lithium aluminium hydride
LC/MS=Liquid chromatographymass spectrometry
MeCN=acetonitrile
MeOH=methanol
$MgSO_4$=magnesium sulfate
MsCl=mesyl chloride or methanesulfonyl chloride
MTBE=methyl tert-butyl ether
MW=microwave irradiation
$NaBH_3CN$=sodium cyanoborohydride
$NaHCO_3$=sodium bicarbonate
$Na(OAc)_3BH$=Sodium triacetoxyborohydride
NMR=nuclear magnetic resonance
ON=overnight
$Pd(dppf)Cl_2$=1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride
$Pd(PPh_3)_4$=tetrakis(triphenylphosphine)palladium(0)
r.t.=room temperature
SPhos Pd G3=[(2-Di-cyclohexylphosphino-3,6-dimethoxy-2',4',6'-triisopropyl-1,1'-biphenyl)-2-(2'-amino-1,1'-biphenyl)]palladium(II) methanesulfonate methanesulfonate
SPhos Pd G4=Methanesulfonato(2-dicyclohexylphosphino-3,6-dimethoxy-2',4',6'-triisopropyl-1,1'-biphenyl)(2'-methylamino-1,1'-biphenyl-2-yl)palladium(II)
TBAF=Tetra-n-butylammonium fluoride,
TEA=triethylamine
TFA=trifluoroacetic acid
THF=tetrahydrofuran
TLC=thin layer chromatography

The following example schemes are provided for the guidance of the reader, and collectively represent an example method for making the compounds provided herein. Furthermore, other methods for preparing compounds of the disclosure will be readily apparent to the person of ordinary skill in the art in light of the following reaction schemes and examples. The skilled artisan is thoroughly equipped to prepare these compounds by those methods given the literature and this disclosure. The compound numberings used in the synthetic schemes depicted below are meant for those specific schemes only, and should not be construed as or confused with same numberings in other sections of the application. Unless otherwise indicated, all variables are as defined above.

General Procedures

Compounds of Formula I of the present disclosure can be prepared as depicted in Scheme 1.

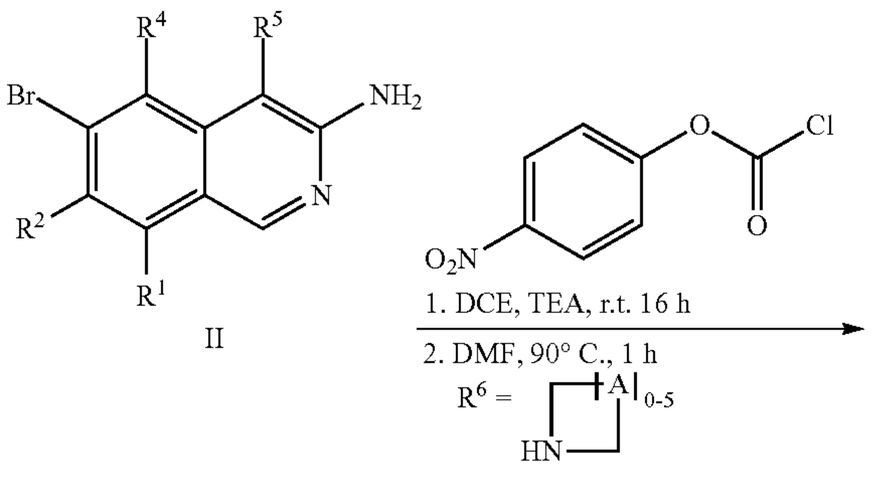
Scheme 1



Scheme 1 describes a method for preparation of isoquinoline-3-carboxamide derivatives (IX) by first coupling the amine with a variety of acids (III) to produce amide IV. The bromo derivative IV is then reacted with bis(pinacolato) diboron to give the pinacol ester (V). Suzuki coupling with a variety of 5-membered heteroaryl bromides (VIII) yields the desired R^3 substituted isoquinoline IX. Alternatively, the bromo derivative IV is Suzuki coupled with a variety of 5-membered heteroaryl pinacol esters (VI) or coupled to a variety of 5-membered heteroaryl stannanes (VII) to produce the final R^3 substituted isoquinoline IX.

In some embodiments, compounds of Formula I of the present disclosure can be prepared as depicted in Scheme 2.

Scheme 2



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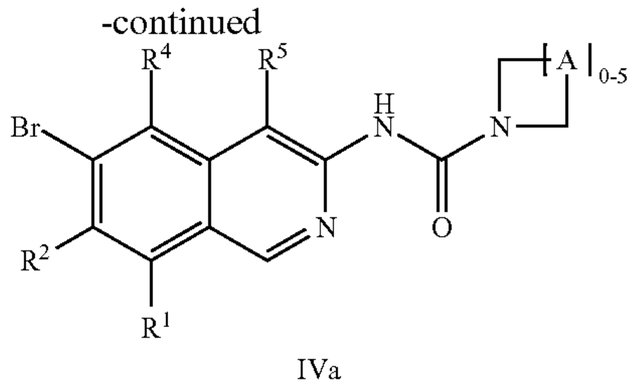
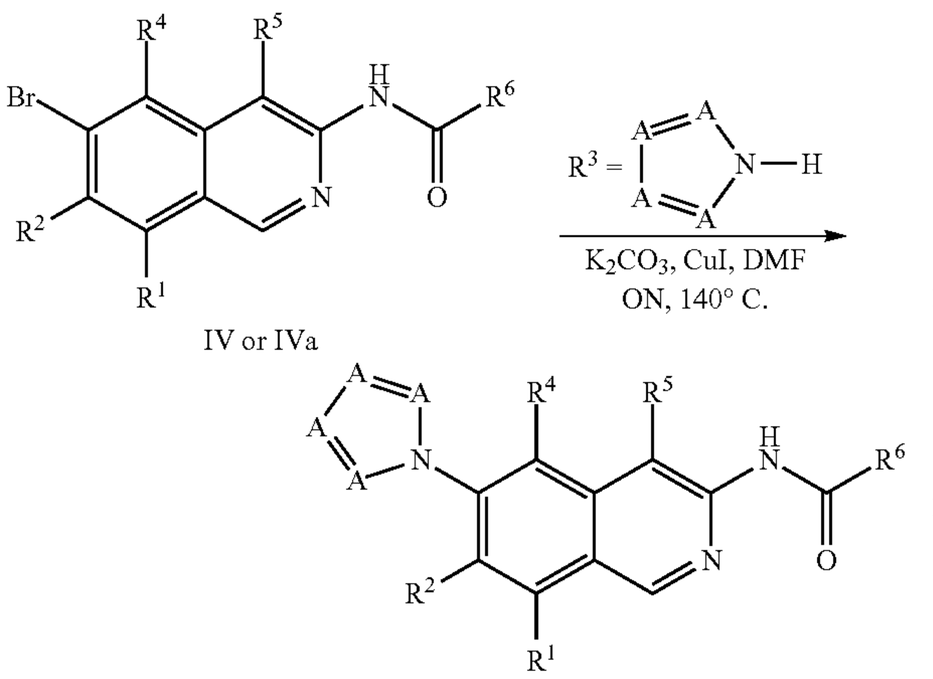


A = C, N, O, or S,
wherein C or N may be substituted
as defined for R^6 herein

Scheme 2 describes a method for preparation of isoquinoline-3-carboxamide intermediate (IVa) by first coupling the amine 4-nitrophenyl carbonochloridate followed by coupling with a variety of R^6 NH heterocyclyls. Intermediate IVa could then be used in place of IV in Scheme 1 or 3.

In other embodiments, compounds of Formula I of the present disclosure can be prepared as depicted in Scheme 3.

Scheme 3



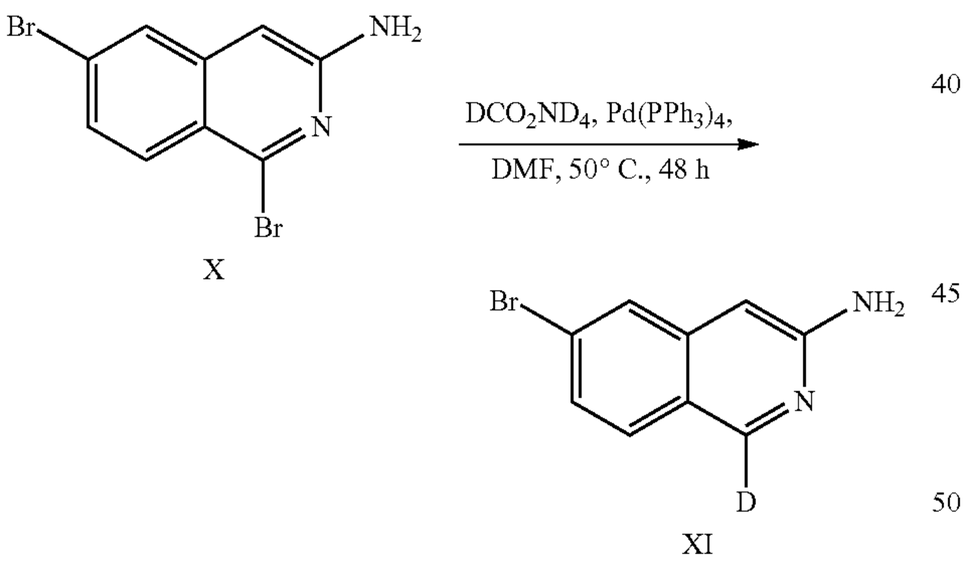
A = N or C, wherein N or C may be substituted as defined for R^3 herein

Scheme 3 describes a method for preparation of isoquinoline-3-carboxamide derivatives (IXa) starting with bromo intermediate IV or IVa and couple with the nitrogen of a variety of R^3 NH heteroaryls to produce the final R^3 substituted isoquinoline IXa.

Illustrative Compound Examples

Preparation of intermediate 6-bromoisoquinolin-1-d-3-amine (XI) is depicted below in Scheme 4.

Scheme 4

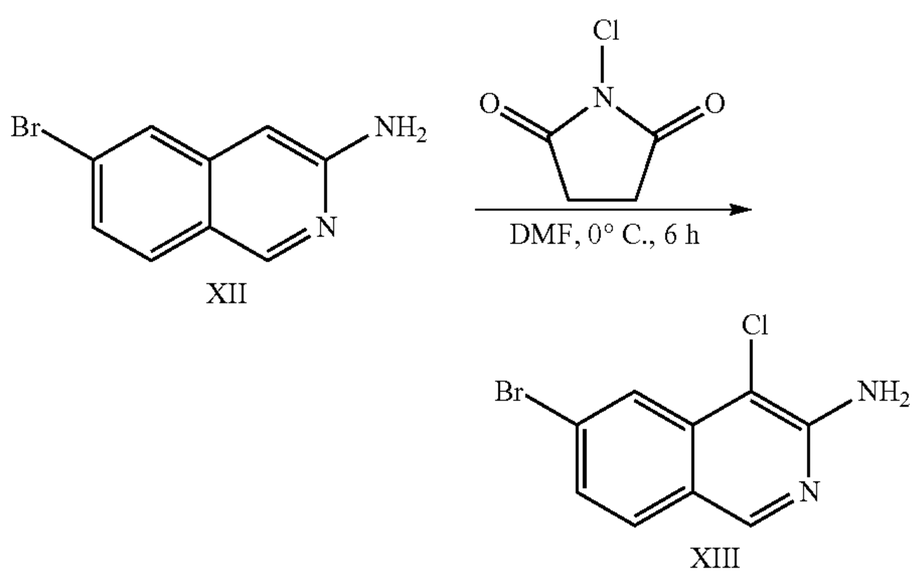


Step 1

To a mixture of 1,6-dibromoisoquinolin-3-amine (X) (0.5 g, 1.66 mmol), ammonium formate-d_5 (0.56 g, 8.28 mmol) and $Pd(PPh_3)_4$ (191.3 mg, 0.170 mmol) in DMF (5 mL) was heated to 50° C. for 48 h. The solvents were concentrated and the residue was suspended in chloroform. The solid was collected by filtration and washed with water and EtOAc. The solid were dried under high vacuo to obtain 6-bromo-1-deuterio-isoquinolin-3-amine (XI) (115 mg, 0.513 mmol, 31.0% yield) as a pale yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 6.11 (2H, s), 6.55 (1H, s), 7.22 (1H, dd, J=8.78, 1.92 Hz), 7.73 (1H, d, J=8.51 Hz), 7.79 (1H, d, J=1.92 Hz); ESIMS found for $C_9H_6DBrN_2$ m/z 224.0 (^{79}BrM+H).

Preparation of intermediate 6-bromo-4-chloroisoquinolin-3-amine (XIII) is depicted below in Scheme 5.

Scheme 5

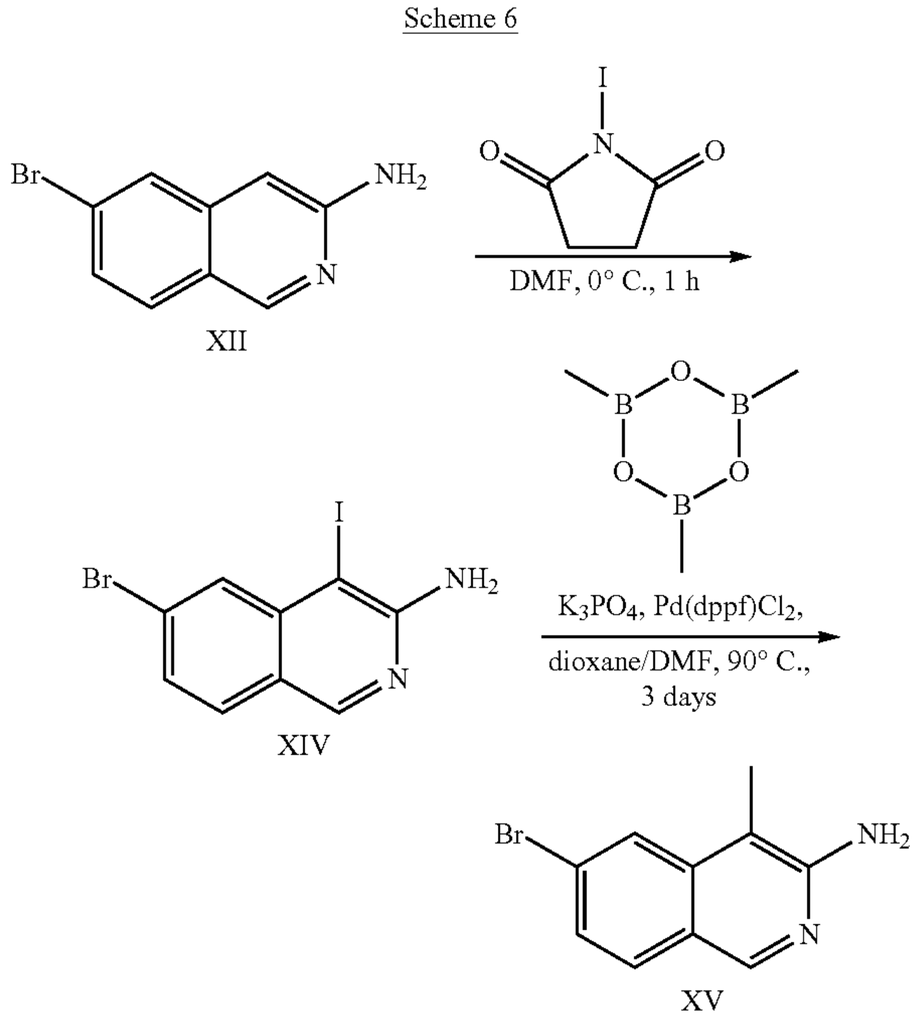


Step 1

To a stirred suspension of 6-bromoisoquinolin-3-amine (XII) (1.0 g, 4.48 mmol) in DMF (15 mL) at 0° C. was added 1-chloropyrrolidine-2,5-dione (598.6 mg, 4.48 mmol) portionwise. The mixture was stirred at 0° C. for 6 h. The reaction mixture was added to water (150 mL), stirred for 1 h and the resulting solids were collected by filtration and air dried overnight to obtain 6-bromo-4-chloro-isoquinolin-3-amine (XIII) (922 mg, 3.58 mmol, 79.9% yield) as a beige solid which was used for next step without purification. ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 6.55 (2H, s), 7.40 (1H, dd, J=8.64, 1.78 Hz), 7.88 (1H, d, J=8.51 Hz), 7.90 (1H, d, J=1.10 Hz), 8.86 (1H, s); ESIMS found for $C_9H_6BrClN_2$ m/z 256.9 (^{79}BrM+H).

Preparation of intermediate 6-bromo-4-methylisoquinolin-3-amine (XV) is depicted below in Scheme 6.

Scheme 6



Step 1

To a stirred suspension of 6-bromoisoquinolin-3-amine (XII) (2. g, 8.97 mmol) in DMF (25.1 mL) at 0° C. was added 1-iodopyrrolidine-2,5-dione (2.02 g, 8.97 mmol) portionwise, The mixture was stirred at 0° C. for 1 hr. LC-MS

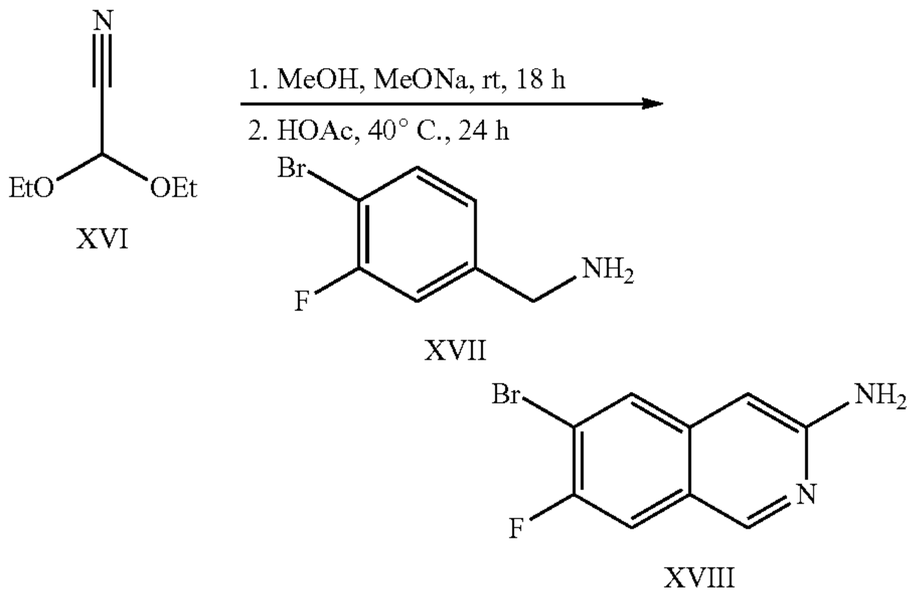
of the mixture showed completion of the reaction and the desired product. The solvent was removed under vacuum, the residue was purified by C18 Silica gel (240 g) [0→100% H_2O/MeCN (0.1% Formic acid)] to produce 6-bromo-4-iodo-isoquinolin-3-amine (XIV) (1.95 g, 5.58 mmol, 62.2% yield) as a brown solid. ^1H NMR (499 MHz, DMSO-d_6) δ ppm 6.41 (2H, br s), 7.40 (1H, dd, J=8.64, 1.78 Hz), 7.76-7.81 (1H, m), 7.82 (1H, d, J=8.51 Hz), 8.81 (1H, s); ESIMS found for $C_9H_6BrIN_2$ m/z 348.9 (^{79}BrM+H).

Step 2

A stirred solution of 6-bromo-4-iodo-isoquinolin-3-amine (XIV) (1.0 g, 2.87 mmol), 2,4,6-trimethyl-1,3,5,2,4,6-trioxatriborinane (0.72 g, 2.87 mmol), $Pd(dppf)Cl_2$ (0.23 g, 0.29 mmol), and K_3PO_4 (5.73 mL, 5.73 mmol) in 1,4-dioxane (10 mL) was heated to 90° C. for 3 days. The solvent was removed under high vacuum and the residue was purified by C18 silica gel (240 g) [0→20% H_2O/MeCN (0.1% Formic acid)] to produce 6-bromo-4-methyl-isoquinolin-3-amine (XV) (74 mg, 0.312 mmol, 10.9% yield) as an off-white solid. ^1H NMR (499 MHz, DMSO-d_6) δ ppm 2.23 (3H, br s), 5.91 (2H, br s), 7.27 (1H, br d, J=2.20 Hz), 7.71-7.82 (1H, m), 7.92 (1H, br s), 8.72 (1H, br s); ESIMS found for $C_{10}H_9BrN_2$ m/z 239.0 (^{81}BrM+H).

Preparation of intermediate 6-bromo-7-fluoroisoquinolin-3-amine (XVIII) is depicted below in Scheme 7.

Scheme 7



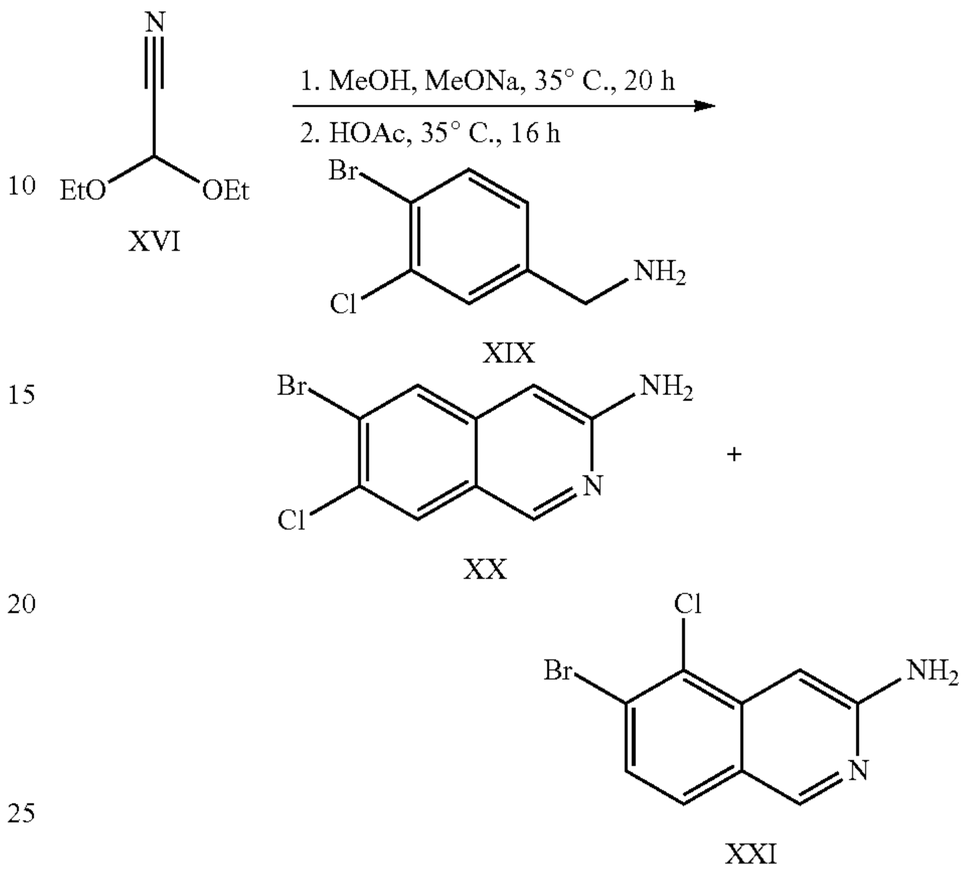
XVI XVII XVIII

Step 1

To a vial was added 2,2-diethoxyacetonitrile (XVI) (1.0 g, 7.74 mmol) dissolved MeOH (7.74 mL) followed by addition of MeONa/MeOH (0.18 mL, 0.77 mmol) dropwise. The reaction was stirred at room temperature for 20 h. HOAc (44.3 μL, 0.77 mmol) was added until pH=7-8 (using pH strips). (4-Bromo-3-fluoro-phenyl)methanamine hydrochloride (XVII) (1.86 g, 7.74 mmol) was added and stirred at 40° C. for 4 h. The solvent was removed under vacuum. Sulfuric acid (12.6 mL, 232.3 mmol) was added and stirred at 40° C. for 16 h. NH_4OH (30.8 mL, 240.0 mmol) was added dropwise at 0° C. The solvent was removed under vacuum and the residue was purified by C18 silica gel (240 g) [0→50% H_2O/MeCN (0.1% Formic acid)] to produce 6-bromo-7-fluoro-isoquinolin-3-amine (XVIII) (1.33 g, 5.50 mmol, 71.1% yield) as an off-white solid. ^1H NMR (499 MHz, DMSO-d_6) δ ppm 6.07 (2H, s), 6.61 (1H, s), 7.76 (1H, d, J=9.33 Hz), 8.01 (1H, d, J=6.86 Hz), 8.80 (1H, s); ESIMS found for $C_9H_6BrFN_2$ m/z 242.9 (^{81}BrM+H).

Preparation of intermediates 6-bromo-7-chloroisoquinolin-3-amine (XX) and 6-bromo-5-chloroisoquinolin-3-amine (XXI) is depicted below in Scheme 8.

Scheme 8



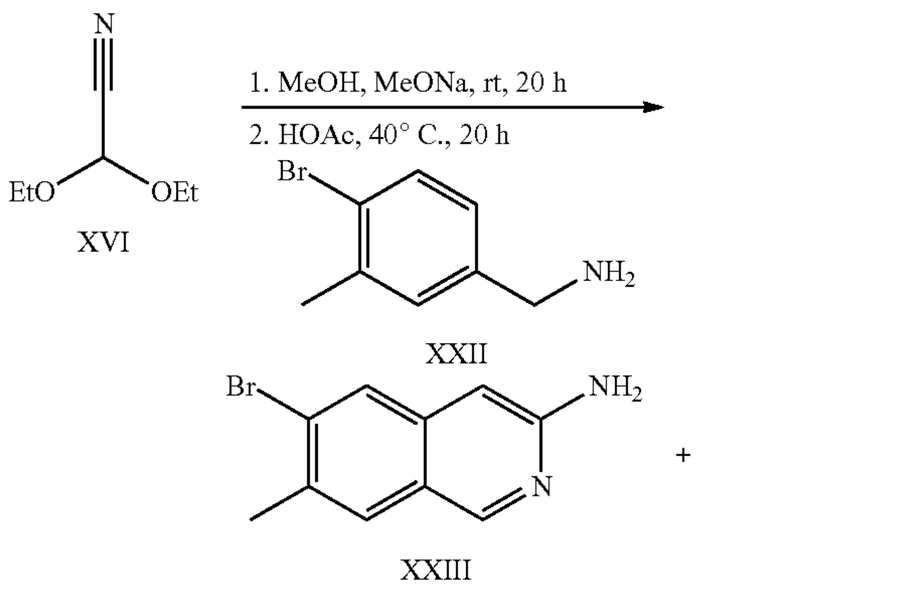
XVI XIX XX XXI

Step 1

To a stirred solution of 2,2-diethoxyacetonitrile (XVI) (0.59 g, 4.57 mmol) in a vial containing MeOH (4.57 mL) was added MeONa (0.1 mL, 0.46 mmol) dropwise. The reaction was stirred at 35° C. for 20 h. HOAc was added (26.1 μL, 0.46 mmol) (checked that the pH is 7-8 using pH strips) followed by (4-bromo-3-chloro-phenyl)methanamine (XIX) (1.01 g, 4.57 mmol). The mixture was stirred at 35° C. for 40 h. The solvent was removed under vacuum. Sulfuric Acid (7.43 mL, 137.0 mmol) was then added and stirred at 35° C. for 16 h. NH_4OH (60.6 mL, 141.6 mmol) was added at 0° C. The reaction was filtered through Celite and purified by C18 silica gel (240 g) [0→30% H_2O/MeCN (0.1% Formic acid)] to produce a 1:1 mixture (by nmr) of 6-bromo-7-chloro-isoquinolin-3-amine (XX) and 6-bromo-5-chloroisoquinolin-3-amine (XXI) (633.7 mg, 2.46 mmol, 53.9% yield). ^1H NMR (499 MHz, DMSO-d_6) δ ppm 6.23 (2H, s), 6.46 (2H, s), 6.57 (1H, s), 6.83 (1H, s), 7.40 (1H, d, J=8.51 Hz), 7.74 (1H, d, J=8.51 Hz), 8.05 (1H, s), 8.09 (1H, s), 8.81 (1H, s), 8.88 (1H, s); ESIMS found for $C_9H_6BrClN_2$ m/z 256.9 (^{79}BrM+H).

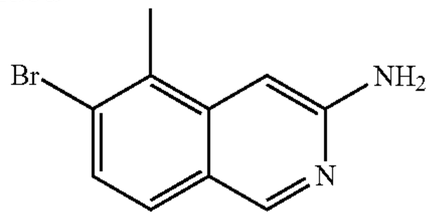
Preparation of intermediates 6-bromo-7-methylisoquinolin-3-amine (XXIII) and 6-bromo-5-methylisoquinolin-3-amine (XXIV) is depicted below in Scheme 9.

Scheme 9



XVI XXII XXIII

-continued



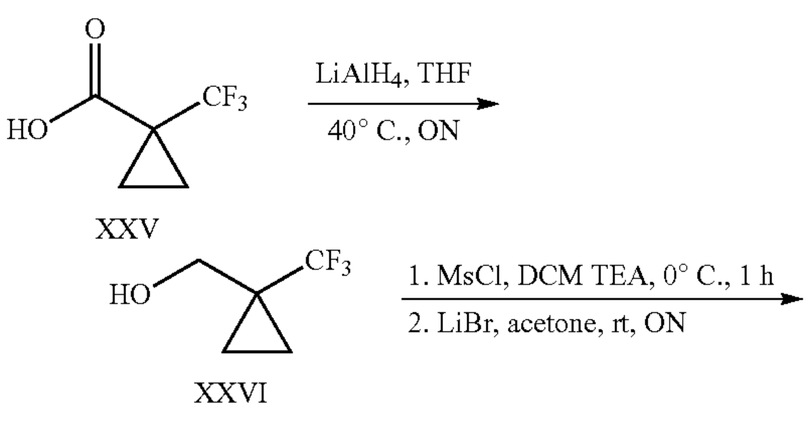
XXIV

Step 1

To a stirred solution of 2,2-diethoxyacetonitrile (XVI) (0.33 g, 2.52 mmol) in a vial containing MeOH (2.52 mL) was added MeONa (0.23 mL, 0.25 mmol) dropwise. The reaction was stirred at 22° C. for 20 h. HOAc was added (14.4 μL, 0.25 mmol) (checked that the pH is 7-8 using pH strips) followed by (4-bromo-3-methyl-phenyl)methanamine (XXII) (0.5 g, 2.52 mmol). The mixture was stirred at 40° C. for 40 h. The solvent was removed under vacuum. Sulfuric Acid (4.09 mL, 75.49 mmol) was then added and stirred at 40° C. for 16 h. NH_4OH (33.4 mL, 78 mmol) was added at 0° C. The reaction was filtered through Celite and purified by C18 silica gel (240 g) [0→30% H_2O/MeCN (0.1% Formic acid)] to produce a 1:1 mixture (by nmr) of 6-bromo-7-methylisoquinolin-3-amine (XXIII) and 6-bromo-5-methylisoquinolin-3-amine (XXIV) (378 mg, 1.59 mmol, 63.4% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 2.40 (3H, s), 2.52 (3H, s), 5.96 (2H, s), 6.12 (1H, s), 6.54 (1H, s), 6.71 (1H, s), 7.27 (1H, d, J=8.78 Hz), 7.58 (1H, d, J=8.78 Hz), 7.73 (1H, s), 7.86 (1H, s), 8.74 (1H, s), 8.79 (1H, s); ESIMS found for $C_{10}H_9BrN_2$ m/z 237.0 (^{79}BrM+H).

Preparation of intermediate 1-(bromomethyl)-1-(trifluoromethyl) cyclopropane (XXVII) is depicted below in Scheme 10.

Scheme 10



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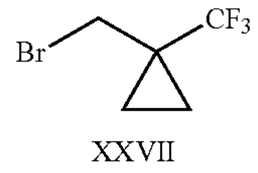


XXVII

Step 1

1-(Trifluoromethyl)cyclopropane-1-carboxylic acid (XXV) (3.7334 g, 24.23 mmol) was dissolved in THF (162 mL) and cooled to 0° C. LAH (1.1614 g, 29.07 mmol) was then added and the reaction heated to 40° C. overnight. The reaction was cooled to 0° C. Water (2 mL) was added to quench the reaction followed by 2 N NaOH (0.3 mL). The reaction was stirred forming a precipitate which was filtered off and washed with ether. The aqueous phase was removed and the organic phase was washed with brine, dried, and carefully concentrated to give (1-(trifluoromethyl)cyclopropyl)methanol (XXVI) (1.5376 g, 10.98 mmol, 45.3% yield) as a clear, volatile liquid.

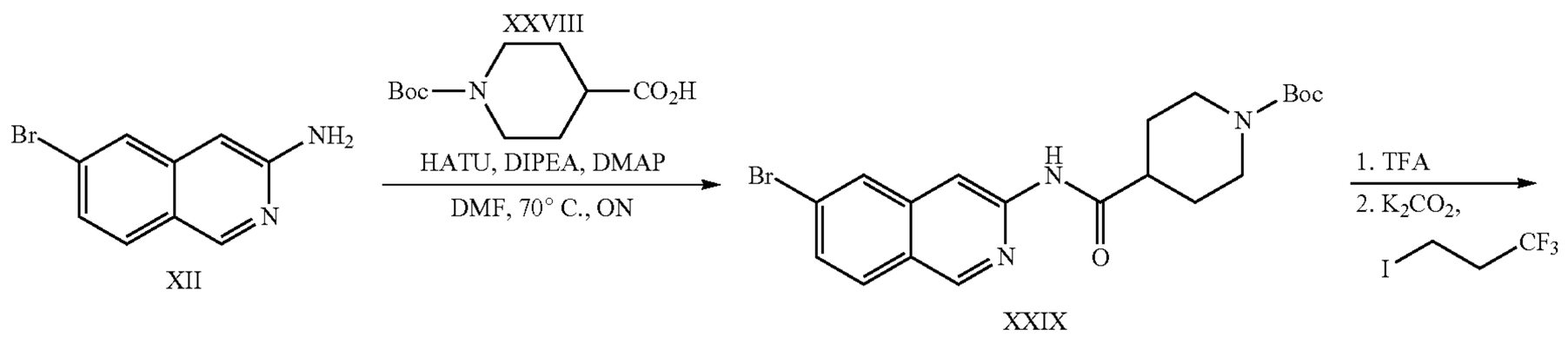
Step 2

To a solution of (1-(Trifluoromethyl)cyclopropyl)methanol (XXVI) (1.6 g, 11.42 mmol) in DCM (23 mL) was added Et_3N (1.9 mL, 13.7 mmol). The reaction was cooled to 0° C. and MsCl was added dropwise. The reaction was stirred at 0° C. for 1 h. The reaction was poured into water, and extracted with DCM. The organic phase was separated, washed with brine, dried, and concentrated. The crude mesylate was then dissolved in acetone (22 mL). LiBr (4.96 g, 57.1 mmol) was added, and the reaction stirred at room temperature overnight. The acetone was carefully removed, and the residue was partitioned between water and ether. The aqueous phase was separated and reextracted with ether. The organic phases were combined, washed with brine, dried, and carefully concentrated to give 1-(bromomethyl)-1-(trifluoromethyl)cyclopropane (XXVII) (1.2867 g, 6.34 mmol, 55.5% yield) as a gold liquid with residual amounts of acetone. ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.04 (2H, tquin, J=5.17, 5.17, 1.74, 1.74, 1.74, 1.74 Hz), 1.23-1.27 (2H, m), 3.77 (2H, s).

Example 1

Preparation of N-(6-(1-methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)-1-(3,3,3-trifluoropropyl)piperidine-4-carboxamide (271) is depicted below in Scheme 11.

Scheme 11



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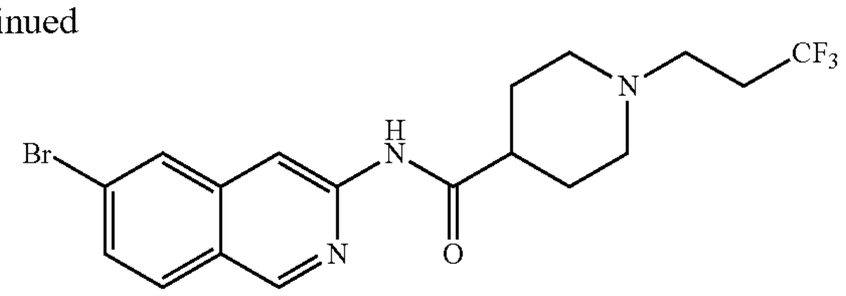
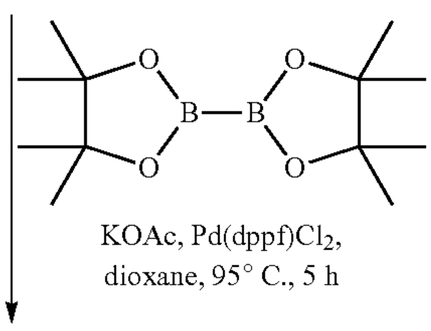
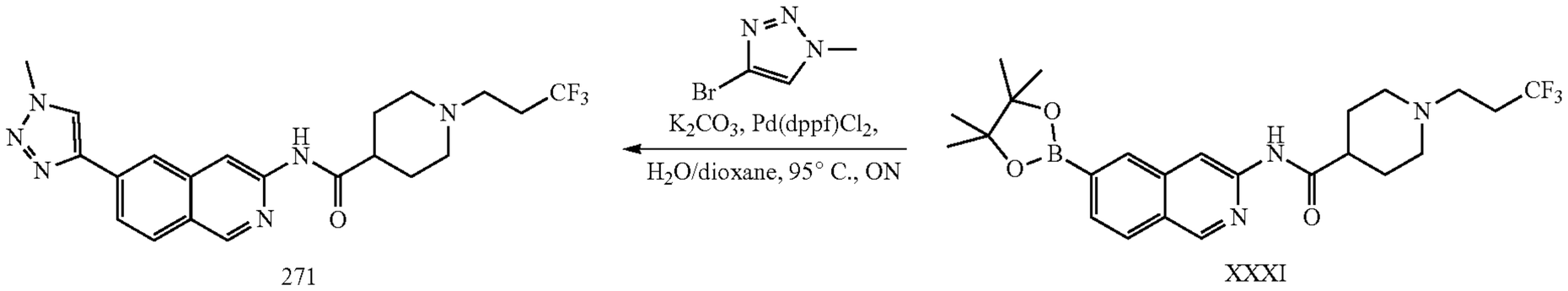


XXX



XXXII



271

XXXI

Step 1

To a stirred solution of 1-(tert-butoxycarbonyl)piperidine-4-carboxylic acid (XXVIII) (1.542 g, 6.72 mmol) and HATU (2.56 g, 6.72 mmol) was added DIPEA (2.349 mL, 13.45 mmol). After 10 min, 6-bromoisoquinolin-3-amine (XII) (1 g, 4.48 mmol) was added followed by the addition of DMAP (0.110 g, 0.897 mmol) and the mixture was heated to 70° C. overnight. The LC/MS of mixture showed complete conversion of the amine to the product. The solvents were concentrated in vacuo, the residue taken into EtOAc, washed with water, sat. aq. $NaHCO_3$ and brine solution. The organic layer was dried over anhydrous Na_2SO_4, solvents removed in vacuo and the residue was dried under high vacuo to obtain crude tert-butyl 4-((6-bromoisoquinolin-3-yl)carbamoyl)piperidine-1-carboxylate (XXIX) as a brown gummy solid (2.29 g, 5.27 mmol, 11.8% yield). Used for next step without purification.

Step 2

To a stirred solution of tert-butyl 4-((6-bromoisoquinolin-3-yl)carbamoyl)piperidine-1-carboxylate (XXIX) (1.0 g, 2.302 mmol) in DCM (4.0 mL) was added TFA (4.0 mL, 51.9 mmol) dropwise and the mixture was stirred at room temperature for 2 h. The solvent were evaporated in vacuo, the residue was neutralized with 7 N NH_3/MeOH, concentrated and dried under high vacuo to obtain N-(6-bromoisoquinolin-3-yl)piperidine-4-carboxamide as a dark brown solid (0.769 g, 2.302 mmol, 100% yield). Used for next step without purification. ESIMS found for $C_{15}H_{16}BrN_3O$ m/z 336.1 (^{81}BrM+H).

Step 3

To a stirred suspension of N-(6-bromoisoquinolin-3-yl) piperidine-4-carboxamide (0.769 g, 2.30 mmol) and potassium carbonate (1.271 g, 9.20 mmol) in MeCN (10 ml) was added 1,1,1-trifluoro-3-iodopropane (0.270 mL, 2.300 mmol). The mixture was then heated to 90° C. overnight. Another equivalents of 1,1,1-trifluoro-3-iodopropane (0.270 mL, 2.300 mmol) was added and heating continued at 90° C. over a 2^{nd} night. The reaction mixture was absorbed on silica and was purified by ISCO using EtOAc/hexanes (0→100%) and then with $CHCl_3$/MeOH (0→100% to recover unreacted starting material). The pure fractions were combined, concentrated, the residue suspended in diethylether, sonicated and the solid were collected by filtration and dried under high vacuo to obtain N-(6-bromoisoquinolin-3-yl)-1-(3,3,3-trifluoropropyl)piperidine-4-carboxamide (XXX) as an off-white solid (0.31 g, 0.720 mmol, 31.3% yield). ^{1}H NMR (DMSO-d_6, 500 MHz) δ ppm 1.57-1.71 (m, 2H), 1.79 (br d, J=11.80 Hz, 2H), 1.89-2.01 (m, 2H), 2.41-2.60 (m, 5H), 2.88-2.98 (m, 2H), 7.63 (dd, J=8.78, 1.92 Hz, 1H), 8.00 (d, J=8.78 Hz, 1H), 8.18 (d, J=1.37 Hz, 1H), 8.45 (s, 1H), 9.14 (s, 1H), 10.61 (s, 1H); ESIMS found for $C_{18}H_{19}BrF_3N_3O$ m/z 432.3 (^{81}BrM+H).

Step 4

To a solution of N-(6-bromoisoquinolin-3-yl)-1-(3,3,3-trifluoropropyl) piperidine-4-carboxamide (XXX) (0.170 g, 0.395 mmol), bis(pinacolato)diboron (0.150 g, 0.593 mmol), potassium acetate (0.116 g, 1.185 mmol) and Pd(dppf)Cl_2—CH_2Cl_2 adduct (0.032 g, 0.040 mmol) was taken in dioxane (2.5 mL). N_2 gas was bubbled into the mixture for 10 min and then the mixture was heated to 95° C. for 5 h to produce N-(6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoquinolin-3-yl)-1-(3,3,3-trifluoropropyl) piperidine-4-carboxamide (XXXI). ESIMS found for $C_{24}H_{31}BF_3N_3O_3$ m/z 478.1 (M+1). Use for next step without work up or further purification.

Step 5

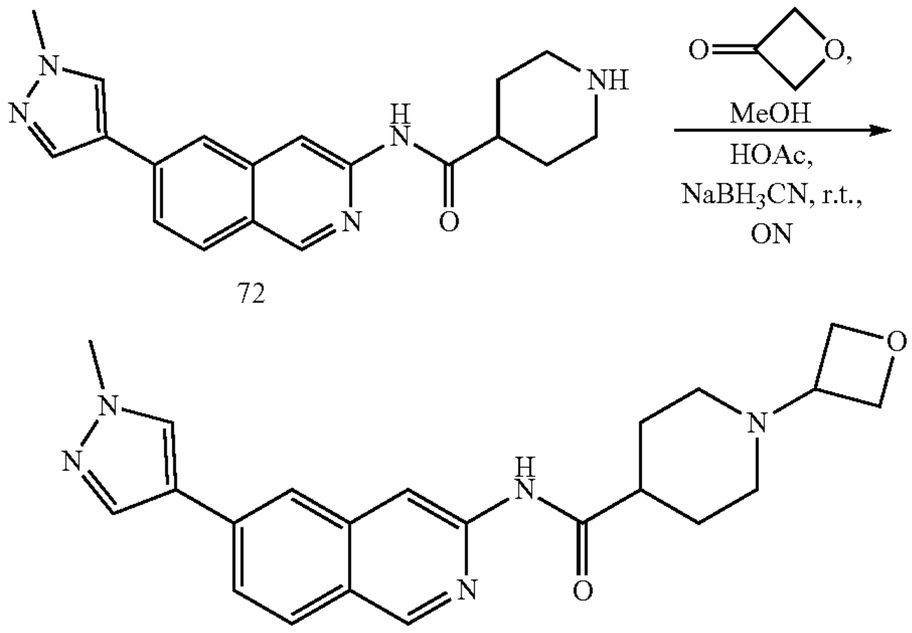
To the above solution was added 4-bromo-1-methyl-1H-1,2,3-triazole (XXXII) (0.064 g, 0.395 mmol), Pd(dppf)Cl_2—CH_2Cl_2 adduct (0.032 g, 0.040 mmol) and 2 M aqueous solution of potassium carbonate (0.395 mL, 0.790 mmol). The reaction mixture was heated overnight at 95° C. The reaction mixture was absorbed on silica and purified by ISCO using $CHCl_3$/7N NH_3 in MeOH (0→5%) followed by preparative TLC to obtain N-(6-(1-methyl-1H-1,2,3-triazol-yl)isoquinolin-3-yl)-1-(3,3,3-trifluoropropyl) piperidine-4-carboxamide (271) as a beige solid (0.011 g, 0.025 mmol,

6.44% yield). ^{1}H NMR (DMSO-d_6, 500 MHz) δ ppm 1.60-1.73 (m, 2H), 1.76-1.84 (m, 2H), 1.92-2.01 (m, 2H), 2.41-2.60 (m, 5H), 2.94 (br d, J=11.25 Hz, 2H), 4.14 (s, 3H), 8.01 (dd, J=8.51, 1.37 Hz, 1H), 8.11 (d, J=8.51 Hz, 1H), 8.28 (s, 1H), 8.50 (s, 1H), 8.73 (s, 1H), 9.11 (s, 1H), 10.55 (s, 1H); ESIMS found for $C_{21}H_{23}F_3N_6O$ m/z 433.2 (M+1).

Example 2

Preparation of N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-1-(oxetan-3-yl) piperidine-4-carboxamide (86) is depicted below in Scheme 12.

Scheme 12



72

86

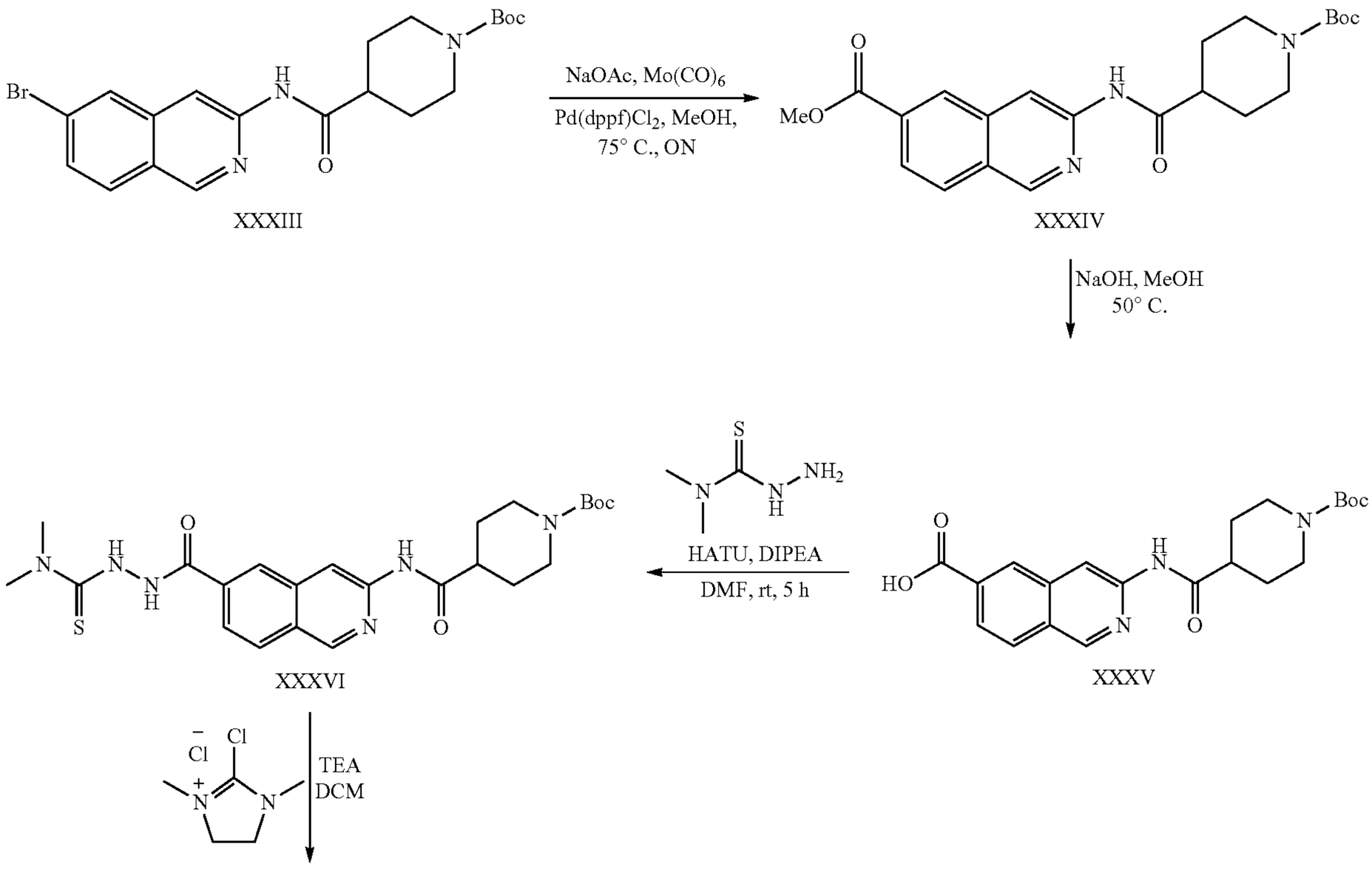
Step 1

To a solution of N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)piperidine-4-carboxamide (72) (0.095 g, 0.283 mmol) in MeOH (1.5 mL) was added oxetan-3-one (0.027 mL, 0.425 mmol) followed by the addition of HOAc (0.081 mL, 1.416 mmol). The mixture was stirred for 20 min, then, sodium cyanoborohydride (0.027 g, 0.425 mmol) was added and the reaction mixture was stirred at room temperature overnight. The solvent was removed in vacuo, the residue partitioned between EtOAc/sat. aq. $NaHCO_3$, the organic layer separated, washed with water and brine. The organic layer was dried over anhydrous Na_2SO_4, solvents removed in vacuo and the crude product was purified by ISCO (0→5% $CHCl_3$/7 N NH_3 in MeOH). The pure fractions were combined, concentrated, the residue suspended in DCM, sonicated and the solids were collected by filtration to obtain N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-1-(oxetan-3-yl)piperidine-4-carboxamide (86) off-white solid (62.0 mg, 0.158 mmol, 56.0% yield). ^{1}H NMR (DMSO-d_6, 500 MHz) δ ppm 1.62-1.73 (m, 2H), 1.74-1.86 (m, 4H), 2.52-2.60 (m, 1H), 2.71-2.80 (m, 2H), 3.38 (quin, J=6.45 Hz, 1H), 3.90 (s, 3H), 4.43 (t, J=6.17 Hz, 2H), 4.53 (t, J=6.59 Hz, 2H), 7.74 (dd, J=8.51, 1.37 Hz, 1H), 8.00 (d, J=8.51 Hz, 1H), 8.04 (s, 1H), 8.08 (s, 1H), 8.35 (s, 1H), 8.45 (s, 1H), 9.02 (s, 1H), 10.48 (s, 1H); ESIMS found for $C_{22}H_{25}N_5O_2$ m/z 392.2 (M+1).

Example 3

Preparation of N-(6-(5-(Dimethylamino)-1,3,4-oxadiazol-2-yl)isoquinolin-3-yl)piperidine-4-carboxamide (1075) and N-(6-(5-(dimethylamino)-1,3,4-oxadiazol-2-yl) isoquinolin-3-yl)-1-methylpiperidine-4-carboxamide (1076) is depicted below in Scheme 13.

Scheme 13



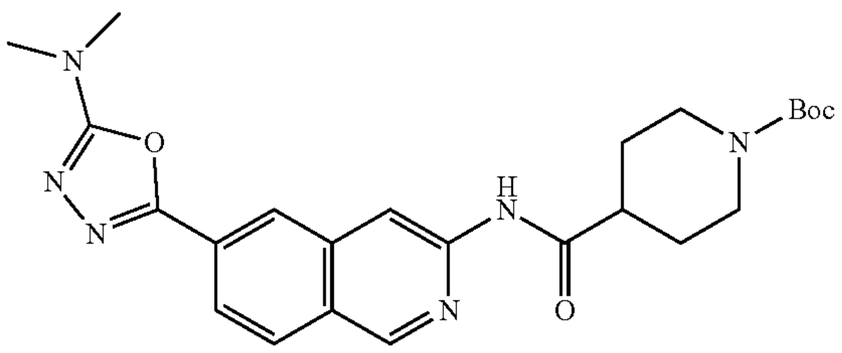
XXXIII

XXXIV

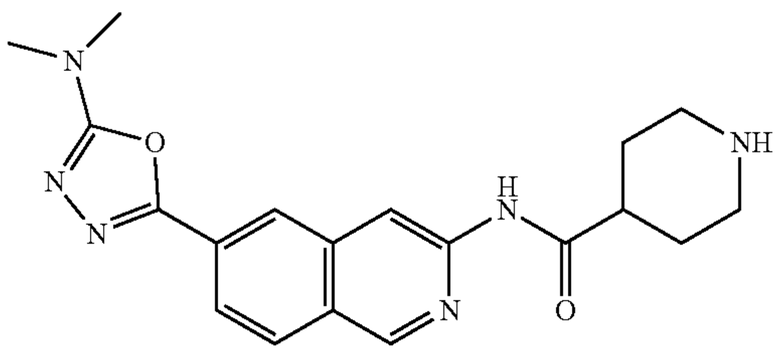
XXXV

XXXVI

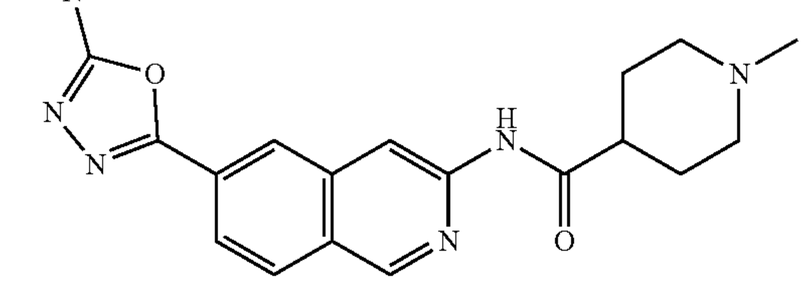
-continued



XXXVII



1075



1076

Step 1

To a mixture of tert-butyl 4-[(6-bromo-3-isoquinolyl) carbamoyl]piperidine-1-carboxylate (XXXIII) (1 g, 2.3 mmol), NaOAc (566.6 mg, 6.91 mmol), molybdenumhexacarbonyl (953 mg, 3.45 mmol) and $Pd(dppf)Cl_2$ (376 mg, 0.46 mmol) in MeOH (20 mL) was heated to 75° C. overnight. The reaction mixture was absorbed on silica gel and was purified by column chromatography using (25%→100% EtOAc/hexanes) to obtain methyl 3-[(1-tert-butoxycarbonylpiperidine-4-carbonyl)amino]isoquinoline-6-carboxylate (XXXIV) (950 mg, 2.30 mmol, 99.8% yield) as a grey solid. ESIMS found for $C_{22}H_{27}N_3O_5$ m/z 414.2 (M+1).

Step 2

To a stirred solution of methyl 3-[(1-tert-butoxycarbonylpiperidine-4-carbonyl)amino]isoquinoline-6-carboxylate (XXXIV) (950.mg, 2.3 mmol) in MeOH (15 mL) was added 2N aqueous solution of NaOH (2.3 mL, 4.6 mmol) and the mixture was heated to 50° C. The reaction mixture was concentrated, the residue taken up in water and acidified with 1N HCl and the resulting solid was collected by filtration, washed with water and dried under high vacuo to obtain 3-[(1-tert-butoxycarbonylpiperidine-4-carbonyl) amino]isoquinoline-6-carboxylic acid (XXXV) (900 mg, 2.25 mmol, 98.1% yield) as a brown solid. ESIMS found for $C_{21}H_{25}N_3O_5$ m/z 400.2 (M+1).

Step 3

To a mixture of 3-[(1-tert-butoxycarbonylpiperidine-4-carbonyl)amino] isoquinoline-6-carboxylic acid (XXXV) (0.5 g, 1.26 mmol), HATU (0.48 g, 1.26 mmol) and N-ethyl-N-isopropyl-propan-2-amine (0.66 mL, 3.77 mmol) in DMF (10 mL) was stirred for 10 min. Then 3-amino-1,1-dimethylthiourea (0.18 g, 1.51 mmol) was added and the mixture was stirred at room temperature for 5 h. The reaction mixture was concentrated, the residue taken in $CHCl_3$, washed with sat. $NaHCO_3$, H_2O and brine. The organic layer was separated and dried ($MgSO_4$) before concentration to dryness to obtain tert-butyl 4-[[6-[(dimethylcarbamothioylamino)carbamoyl]-3-isoquinolyl]carbamoyl]piperidine-1-carboxylate (XXXVI) (600 mg, 1.20 mmol, 95.4% yield) as a brown solid which was used for next step without purification. ESIMS found for $C_{24}H_{32}N_6O_4S$ m/z 501.2 (M+1).

Step 4

To a mixture of tert-butyl 4-[[6-[(dimethylcarbamothioylamino)carbamoyl]-3-isoquinolyl]carbamoyl]piperidine-1-carboxylate (XXXVI) (600 mg, 1.2 mmol), 2-chloro-1,3-dimethyl-4,5-dihydroimidazol-1-ium chloride (405.2 mg, 2.4 mmol) and N,N-diethylethanamine (0.5 mL, 3.6 mmol) in DCM (10 mL) was stirred overnight at room temperature. Reaction mixture was concentrated and the residue was purified by column chromatography (0→10% 7N—NH_3-MeOH/$CHCl_3$) to obtain tert-butyl 4-[[6-[5-(dimethylamino)-1,3,4-oxadiazol-2-yl]-3-isoquinolyl] carbamoyl]piperidine-1-carboxylate (XXXVII) (60 mg, 0.129 mmol, 10.7% yield) as a brown solid. ESIMS found for $C_{24}H_{30}N_6O_4$ m/z 467.2 (M+1).

Step 5

To a stirred solution of tert-butyl 4-[[6-[5-(dimethylamino)-1,3,4-oxadiazol-2-yl]-3-isoquinolyl]carbamoyl]piperidine-1-carboxylate (XXXVII) (60 mg, 0.130 mmol) in DCM (2 mL) was added TFA (0.2 mL, 2.57 mmol) and the mixture was stirred at room temperature for 5 h. Reaction mixture was concentrated and the residue was absorbed on silica gel, purified by flash column chromatography (0-10% 7N—NH_3-MeOH/$CHCl_3$) to obtain N-[6-[5-(dimethylamino)-1,3,4-oxadiazol-2-yl]-3-isoquinolyl]piperidine-4-carboxamide (1075) (32 mg, 0.087 mmol, 67.9% yield) as a white solid. ^1H NMR (499 MHz, DMSO-d_6) δ ppm 1.54 (2H, qd, J=12.17, 4.12 Hz), 1.71 (2H, br d, J=10.43 Hz), 2.44-2.49 (2H, m), 2.65 (1H, tt, J=11.49, 3.60 Hz), 2.98 (2H, br d, J=12.08 Hz), 3.13 (6H, s), 7.96 (1H, dd, J=8.51, 1.65 Hz), 8.15 (1H, d, J=8.51 Hz), 8.35 (1H, s), 8.59 (1H, s), 9.17 (1H, s), 10.55 (1H, s); ESIMS found for $C_{19}H_{22}N_6O_2$ m/z 367.2 (M+1).

Step 6

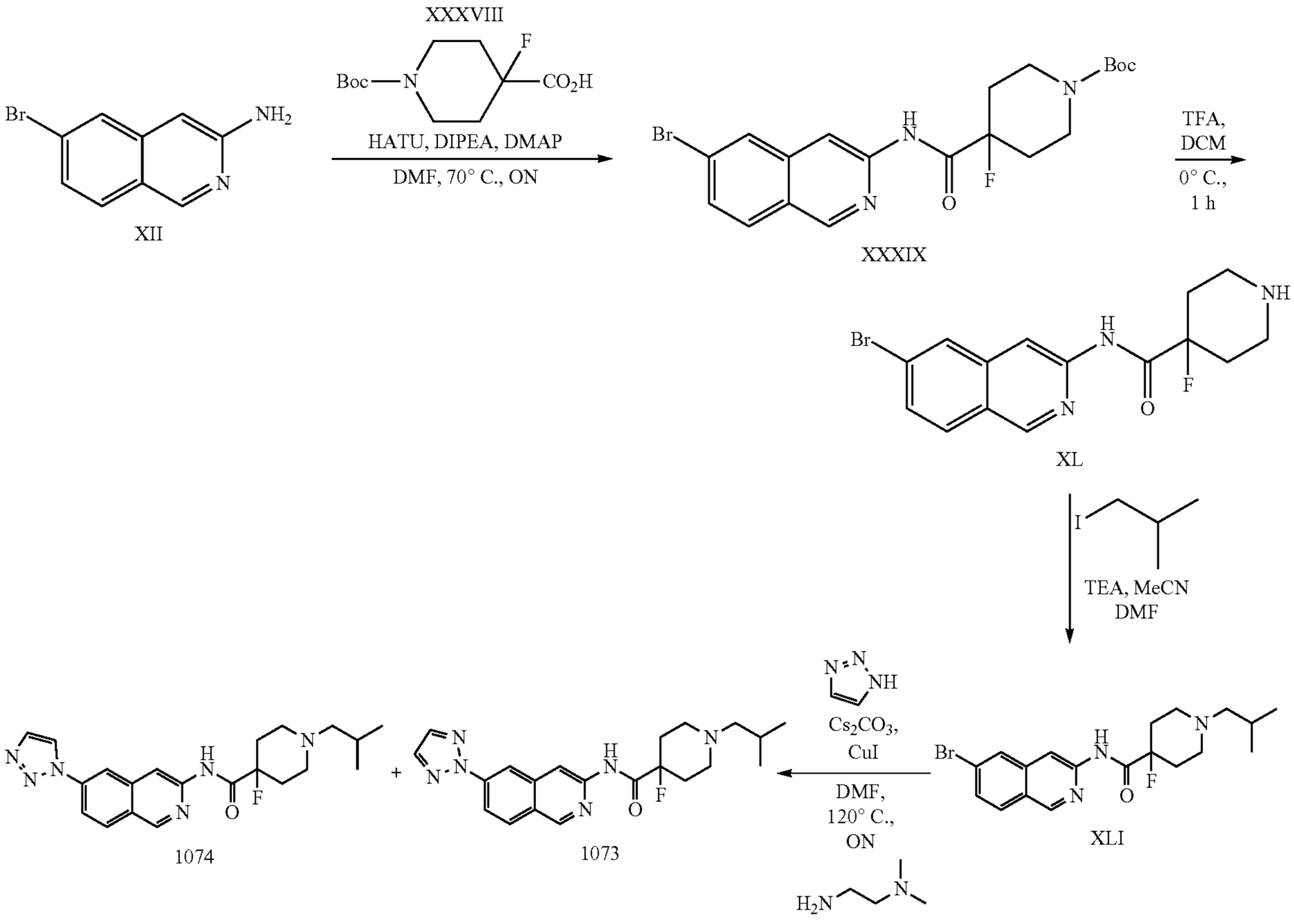
To a mixture of N-[6-[5-(dimethylamino)-1,3,4-oxadiazol-2-yl]-3-isoquinolyl]piperidine-4-carboxamide (1075) (27 mg, 0.070 mmol), $NaBH_3CN$ (14.03 mg, 0.070 mmol)

and catalytic HOAc in MeOH (2 mL) was stirred for 30 min, formaldehyde (2.21 mg, 0.070 mmol) was added and the stirring was continued 2 h. The reaction mixture was quenched with minimum amount of aq. saturated NH_4Cl, concentrated on under vacuum and the residue was adsorbed on silica gel, purified by chromatography (0→20% 7N.NH_3-MeOH/$CHCl_3$) to obtain N-[6-[5-(dimethylamino)-1,3,4-oxadiazol-2-yl]-3-isoquinolyl]-1-methyl-piperidine-4-carboxamide (1076) (25 mg, 0.066 mmol, 89.2% yield) as a white solid. ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.62-1.74 (2H, m), 1.74-1.81 (2H, m), 1.87 (2H, td, J=11.66, 2.20 Hz), 2.16 (3H, s), 2.51-2.56 (1H, m), 2.77-2.85 (2H, m), 3.13 (6H, s), 7.96 (1H, dd, J=8.51, 1.65 Hz), 8.15 (1H, d, J=8.51 Hz), 8.35 (1H, s), 8.59 (1H, s), 9.18 (1H, s), 10.61 (1H, s); ESIMS found for $C_{20}H_{24}N_6O_2$ m/z 381.2 (M+1).

Example 4

Preparation of N-(6-(1H-1,2,3-triazol-1-yl)isoquinolin-3-yl)-4-fluoro-1-isobutylpiperidine-4-carboxamide (1074) and N-(6-(2H-1,2,3-triazol-2-yl)isoquinolin-3-yl)-4-fluoro-1-isobutylpiperidine-4-carboxamide (1075) is depicted below in Scheme 14.

Scheme 14



Step 1

To a mixture of 1-tert-butoxycarbonyl-4-fluoro-piperidine-4-carboxylic acid (XXXVIII) (1.07 mL, 13.99 mmol), HATU (7.09 g, 18.65 mmol) and DIPEA (4.87 mL, 27.97 mmol) in DMF (40 mL) was stirred for 10 min. Then, 6-bromoisoquinolin-3-amine (XII) (2.08 g, 9.32 mmol) and DMAP (0.23 g, 1.86 mmol) was added then the mixture was heated to 80° C. overnight. The reaction mixture was concentrated, the residue partitioned between EtOAc/sat. $NaHCO_3$, organic layer separated, washed with water and brine. The organics were then separated and dried ($MgSO_4$) before concentration to dryness. The crude was then purified by flash column chromatography (0→40% EtOAc/hexanes). The desired fractions were concentrated to dryness en vacuo and recrystallized with hexanes to obtain tert-butyl 4-[(6-bromo-3-isoquinolyl)carbamoyl]-4-fluoro-piperidine-1-carboxylate (XXXIX) (2.94 g, 6.50 mmol, 69.7% yield) as a white solid. ESIMS found for $C_{20}H_{23}BrFN_3O_3$ m/z 452.1 (^{79}BrM+1).

Step 2

To a suspension of tert-butyl 4-[(6-bromo-3-isoquinolyl) carbamoyl]-4-fluoro-piperidine-1-carboxylate (XXXIX) (1.92 g, 4.24 mmol) in DCM (8 mL) was added TFA (8. mL, 103.84 mmol) at 0° C. and the mixture was stirred for 1 h. The solvents were concentrated, triturated with $CHCl_3$ (3×) and the resulting solids were dried under high vacuo to obtain N-(6-bromo-3-isoquinolyl)-4-fluoro-piperidine-4-carboxamide (XL) (1.979 g, 4.24 mmol, 100% yield) as an off-white solid which was used for next step without further purification. ESIMS found for $C_{15}H_{15}BrFN_3O$ m/z 352.0 (^{79}BrM+1).

Step 3

To a suspension of N-(6-bromo-3-isoquinolyl)-4-fluoro-piperidine-4-carboxamide (XL) (1.98 g, 4.24 mmol) in MeCN (20 mL) was added 1-iodo-2-methyl-propane (0.98 mL, 8.48 mmol) and the mixture was stirred for 30 min. The solvents were concentrated, treated with 7N NH_3/MeOH, absorbed on silica gel and purified by column chromatog-

raphy (0→30% $CHCl_3$/10% 7N NH_3 MeOH) to obtain N-(6-bromo-3-isoquinolyl)-4-fluoro-1-isobutyl-piperidine-4-carboxamide (XLI) (1.4 g, 3.43 mmol, 80.9% yield) as a beige solid. ESIMS found for $C_{19}H_{23}BrFN_3O$ m/z 408.1 (^{79}BrM+1).

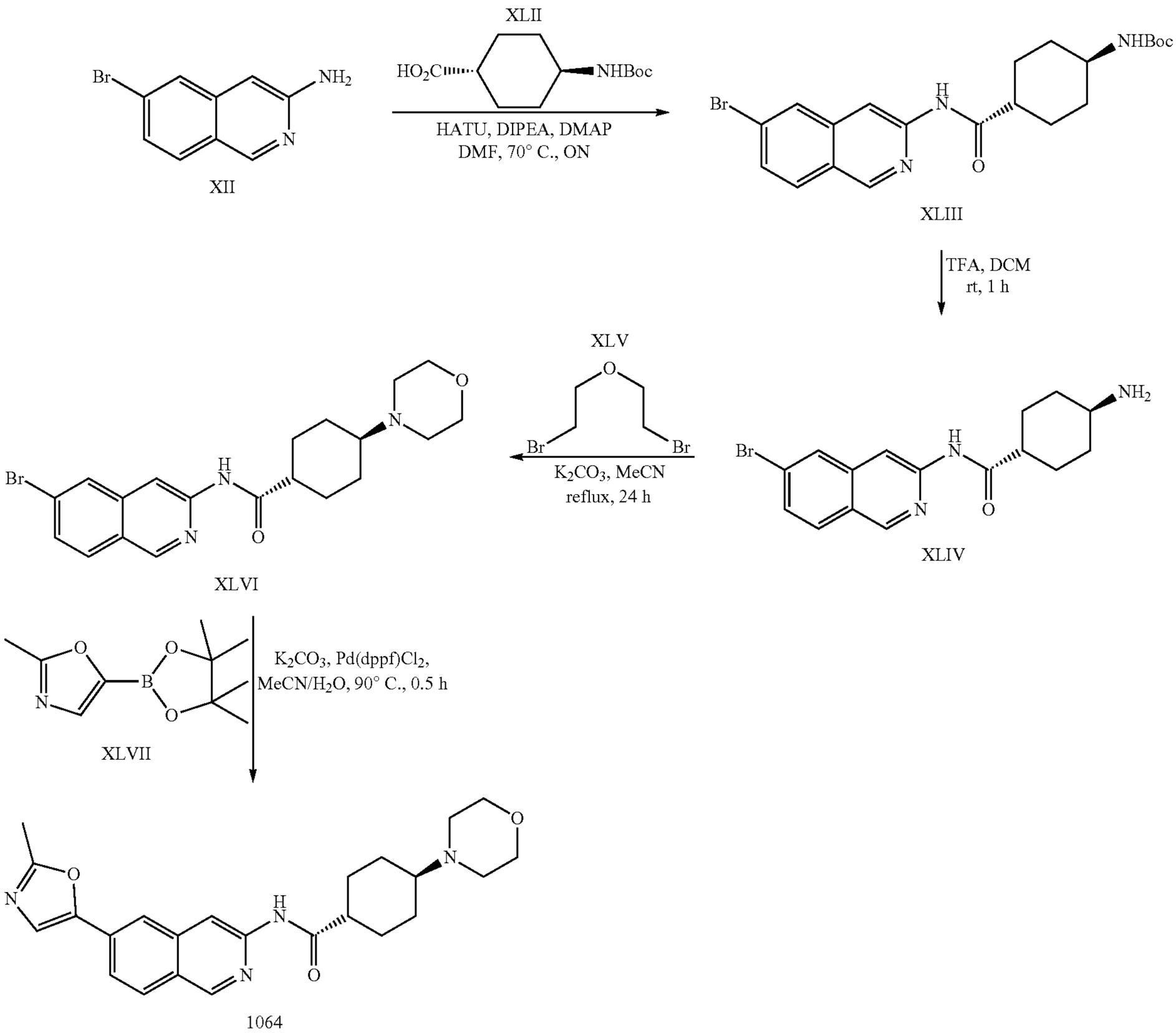
Step 4

To a mixture of N-(6-bromo-3-isoquinolyl)-4-fluoro-1-isobutyl-piperidine-4-carboxamide (XLI) (150 mg, 0.370 mmol), 1H-triazole (0.04 mL, 0.730 mmol), Cs_2CO_3 (239 mg, 0.730 mmol), N,N-dimethylethylenediamine (6.48 mg, 0.070 mmol) and CuI (0. mL, 0.040 mmol) in DMF (2 mL) was purged with N_2 gas for 10 min. The mixture was then heated to 120° C. overnight. The reaction mixture was filtered through Celite and to the filtrates, water was added and extracted with EtOAc. The organics were separated, washed with brine, dried over anhydrous Na_2SO_4, and evaporated under vacuo. The crude products were purified by RP-HPLC. The pure fractions were combined and dried under vacuum to obtain N-(6-(2H-1,2,3-triazol-2-yl)isoquinolin-3-yl)-4-fluoro-1-isobutylpiperidine-4-carboxamide (1073) (3.5 mg, 0.008 mmol, 2.2% yield) as an off-white solid; ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 0.88 (6H, d, J=6.59 Hz), 1.79 (1H, dquin, J=13.55, 6.84, 6.84, 6.84, 6.84 Hz), 1.92-2.02 (2H, m), 2.05-2.21 (6H, m), 2.75-2.82 (2H, m), 8.25 (2H, s), 8.26-8.29 (1H, m), 8.29-8.33 (1H, m), 8.52 (1H, d, J=1.37 Hz), 8.56 (1H, s), 9.25 (1H, s), 10.02 (1H, br d, J=3.29 Hz); ESIMS found for $C_{21}H_{25}FN_6O$ m/z 397.0 (M+1) and N-(6-(1H-1,2,3-triazol-1-yl)isoquinolin-3-yl)-4-fluoro-1-isobutylpiperidine-4-carboxamide (1074) (2 mg, 0.005 mmol, 1.2% yield) as an off-white solid. ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 0.88 (6H, d, J=6.59 Hz), 1.79 (1H, dquin, J=13.46, 6.79, 6.79, 6.79, 6.79 Hz), 1.92-2.02 (2H, m), 2.06-2.12 (2H, m), 2.12-2.21 (4H, m), 2.73-2.83 (2H, m), 8.06 (1H, d, J=1.10 Hz), 8.19 (1H, dd, J=8.92, 2.06 Hz), 8.34 (1H, d, J=9.06 Hz), 8.53 (1H, d, J=1.92 Hz), 8.58 (1H, s), 9.03 (1H, d, J=1.10 Hz), 9.28 (1H, s), 10.07 (1H, br d, J=3.84 Hz); ESIMS found for $C_{21}H_{25}FN_6O$ m/z 397.0 (M+1).

Example 5

Preparation of trans-N-(6-(2-methyloxazol-5-yl)isoquinolin-3-yl)-4-morpholinocyclohexane-1-carboxamide (1064) is depicted below in Scheme 15.

Scheme 15



Step 1

To a mixture of trans-4-(tert-butoxycarbonylamino)cyclohexanecarboxylic acid (XLII) (1.15 mL, 56.04 mmol), HATU (21.31 g, 56.04 mmol), 6-bromoisoquinolin-3-amine (XII) (10. g, 44.83 mmol), and DMAP (1.1 g, 8.97 mmol) in DMF (100 mL) was added DIPEA (23.4 mL, 134.49 mmol). The mixture was stirred at 70° C. overnight. The reaction mixture was cooled before water (800 mL) was added and stirred for ~2 h. The solid was collected by filtration and sequentially washed with aq. sat. NH_4Cl, water and aq. sat. $NaHCO_3$. The solid was dried under high vacuo to obtain tert-butyl trans-N-[4-[(6-bromo-3-isoquinolyl)carbamoyl] cyclohexyl] carbamate (XLIII) (17.87 g, 39.86 mmol, 88.9% yield) as a grey solid which was used for next step without further purification. ESIMS found for $C_{21}H_{26}BrN_3O_3$ m/z 448.1 (^{79}BrM+1).

Step 2

To a stirred solution of tert-butyl trans-N-[4-[(6-bromo-3-isoquinolyl) carbamoyl]cyclohexyl]carbamate (XLIII) (5. g, 11.15 mmol) in DCM (20 mL) was added TFA (10 mL, 129.8 mmol). The mixture was stirred for 1 h at 25° C. The solvent was concentrated and the residue was treated with 7N NH_3/MeOH. The crude product was purified by column chromatography (25→100% $CHCl_3$/10% 7N NH_3 MeOH in $CHCl_3$). The pure fractions were combined, concentrated, the residue suspended in EtOAc, sonicated and the solid was collected by filtration, washed with diethyl ether and dried under high vacuo to obtain trans-4-amino-N-(6-bromo-3-isoquinolyl)cyclohexanecarboxamide (XLIV) (3 g, 8.61 mmol, 77.2% yield) as a beige solid. ESIMS found for $C_{16}H_{18}BrN_3O$ m/z 348.1 (^{79}BrM+1).

Step 3

To a mixture of trans-4-amino-N-(6-bromo-3-isoquinolyl) cyclohexanecarboxamide (XLIV) (550 mg, 1.58 mmol), 1-bromo-2-(2-bromoethoxy)ethane (XLV) (439.53 mg, 1.9 mmol) and K_2CO_3 (654.8 mg, 4.74 mmol) in MeCN (8 mL) was heated to reflux for 24 h. The reaction mixture was concentrated and the residue was taken into DCM, washed with water and brine. The organic layer was then separated and dried ($MgSO_4$) before concentration to dryness. The crude was dissolved in EtOAc, sonicated and the solid was collected by filtration and dried under high vacuo to obtain the desired product trans-N-(6-bromo-3-isoquinolyl)-4-morpholino-cyclohexanecarboxamide (XLVI) (320 mg, 0.765 mmol, 48.4% yield) as an off-white solid. ESIMS found for $C_{20}H_{24}BrN_3O_2$ m/z 418.1 (^{79}BrM+1).

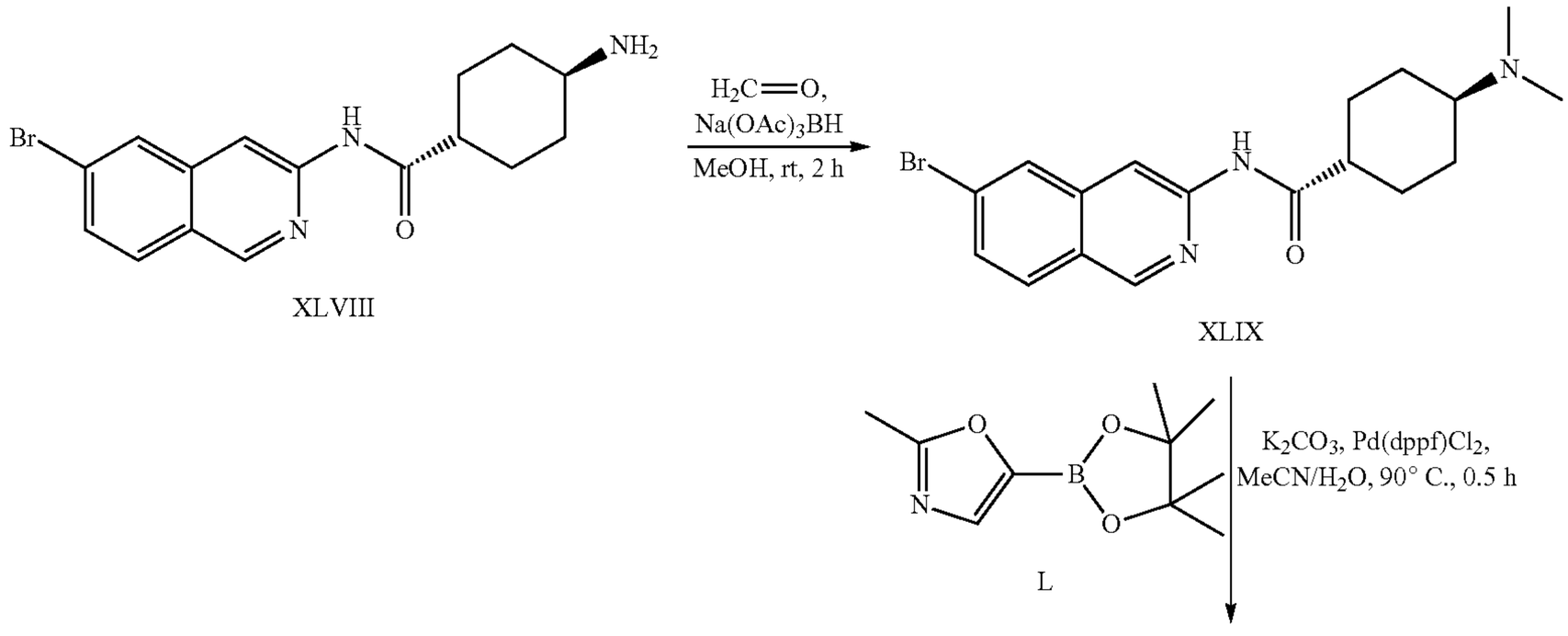
Step 4

To a mixture of 2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) oxazole (XLVII) (62.5 mg, 0.300 mmol), Pd(dppf)Cl_2—CH_2Cl_2 adduct (9.76 mg, 0.010 mmol) and trans-N-(6-bromo-3-isoquinolyl)-4-morpholino-cyclohexanecarboxamide (XLVI) (100 mg, 0.240 mmol) in MeCN (1 mL) was added a 2 M aqueous solution of K_2CO_3 (0.3 mL, 0.600 mmol). N_2 gas was bubbled into the mixture for 10 min and then the solution was heated to 90° C. for 0.5 h. The organic layer was carefully separated, absorbed on silica gel and purified by flash column chromatography (0→40% $CHCl_3$/10% 7N NH_3 in MeOH) followed by preparative TLC. The purified product was suspended in EtOAc, sonicated and the solid was collected by filtration and dried under high vacuo to obtain trans-N-[6-(2-methyl-oxazol-5-yl)-3-isoquinolyl]-4-morpholino-cyclohexanecarboxamide (1064) (18 mg, 0.043 mmol, 17.9% yield) as an off-white solid. ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.16-1.27 (2H, m), 1.42-1.56 (2H, m), 1.91 (4H, br t, J=11.80 Hz), 2.17-2.27 (1H, m), 2.44-2.49 (4H, m), 2.53 (3H, s), 3.26-3.30 (1H, m), 3.54-3.58 (4H, m), 7.78 (1H, s), 7.79-7.83 (1H, m), 8.09 (2H, dd, J=4.80, 3.98 Hz), 8.50 (1H, s), 9.10 (1H, s), 10.51 (1H, s); ESIMS found for $C_{24}H_{28}N_4O_3$ m/z 421.2 (M+1).

Example 6

Preparation of trans-4-(dimethylamino)-N-(6-(2-methyl-oxazol-5-yl) isoquinolin-3-yl)cyclohexane-1-carboxamide (1017) is depicted below in Scheme 16.

Scheme 16



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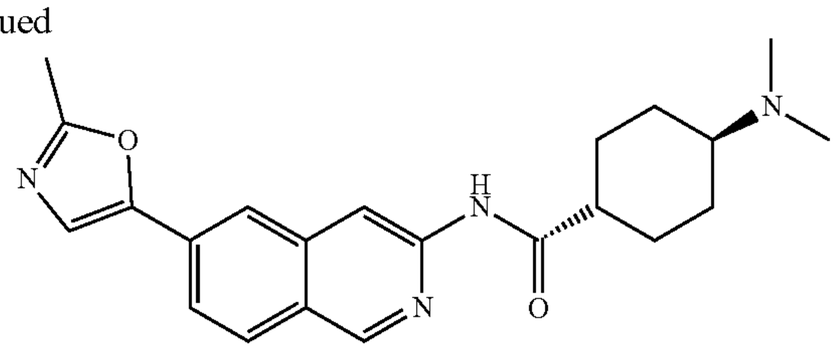


1017

Step 1

To a stirred solution of trans-4-amino-N-(6-bromo-3-isoquinolyl) cyclohexanecarboxamide (XLVIII) (3 g, 8.61 mmol) in MeOH (50 mL) was added formaldehyde (8.64 mL, 42.93 mmol). After 15 min, $Na(OAc)_3BH$ (9.1 g, 42.93 mmol) was added and the mixture was stirred at room temperature for 2 h. The solvents were removed in vacuo, the residue taken in water, basified with 1N NaOH solution and extracted with $CHCl_3$. The organic layer was separated, washed with water and brine, and dried over anhydrous Na_2SO_4. The solvent was concentrated and the crude was suspended in diethyl ether, sonicated and the solid was collected by filtration and dried under high vacuo to obtain the desired product trans-N-(6-bromo-3-isoquinolyl)-4-(dimethylamino)cyclohexanecarboxamide (XLIX) (2.28 g, 6.06 mmol, 70.3% yield) as a beige solid. ESIMS found for $C_{18}H_{22}BrN_3O$ m/z 376.1 (^{79}BrM+1).

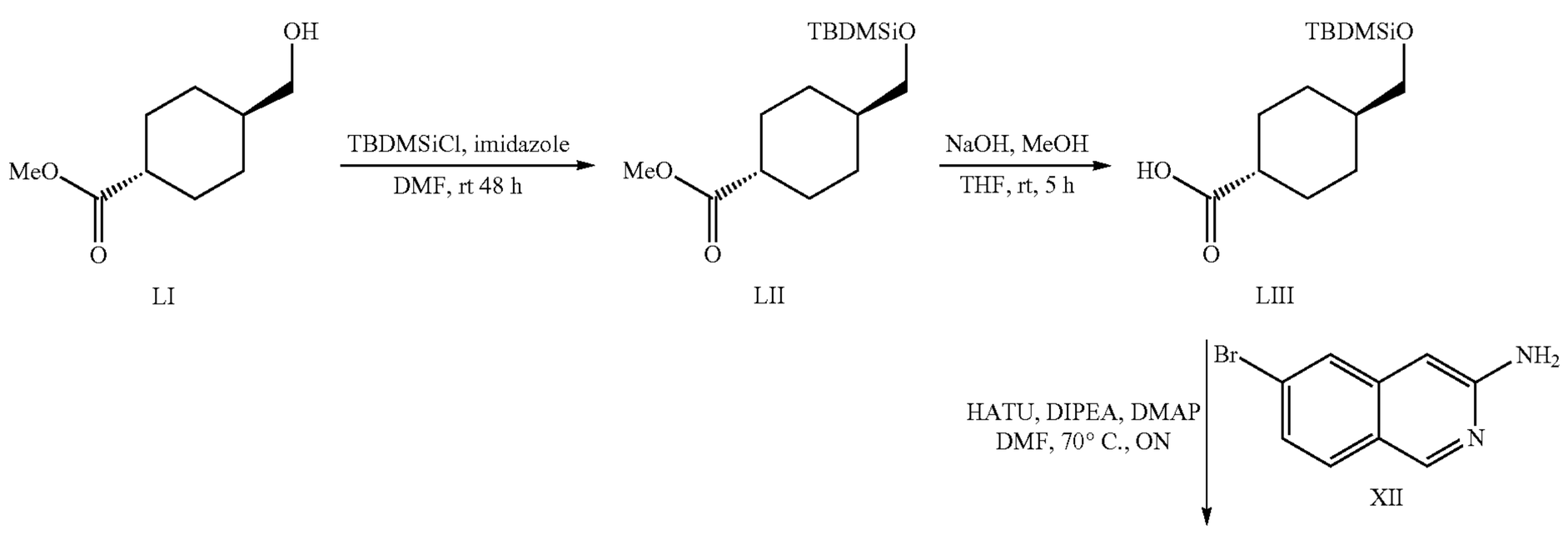
Step 2

To a mixture of 2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) oxazole (L) (138.9 mg, 0.660 mmol), $Pd(dppf)Cl_2$—CH_2Cl_2 adduct (43.4 mg, 0.050 mmol), a 2 M aqueous solution of K_2CO_3 (0.66 mL, 1.33 mmol) and trans-N-(6-bromo-3-isoquinolyl)-4-(dimethylamino)cyclohexanecarboxamide (XLIX) (200 mg, 0.530 mmol) in MeCN (2.5 mL). N_2 gas was bubbled into the mixture for 10 min and then the solution was heated to 110° C. for 30 min in a microwave. The organic layer was carefully separated, absorbed on silica gel and purified by column chromatography (0→50% $CHCl_3$/10%7N NH_3 MeOH in $CHCl_3$). The pure fractions were combined, concentrated and the product was suspended in EtOAc, sonicated and the solid was collected by filtration, washed with diethyl ether and dried under high vacuo to obtain trans-4-(dimethylamino)-N-[6-(2-methyloxazol-5-yl)-3-isoquinolyl]cyclohexanecarboxamide (1017) (92 mg, 0.243 mmol, 45.7% yield) as a beige solid. ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.14-1.23 (2H, m), 1.43-1.54 (2H, m), 1.83-1.95 (4H, m), 2.10-2.16 (1H, m), 2.18 (6H, s), 2.44-2.49 (1H, m), 2.53 (3H, s), 7.78 (1H, s), 7.79-7.84 (1H, m), 8.06-8.13 (2H, m), 8.50 (1H, s), 9.10 (1H, s), 10.49 (1H, s); ESIMS found for $C_{22}H_{26}N_4O_2$ m/z 379.2 (M+1).

Example 7

Preparation of trans-4-((4-methylpiperazin-1-yl)methyl)-N-(6-(oxazol-5-yl) isoquinolin-3-yl)cyclohexane-1-carboxamide (1007) is depicted below in Scheme 17.

Scheme 17



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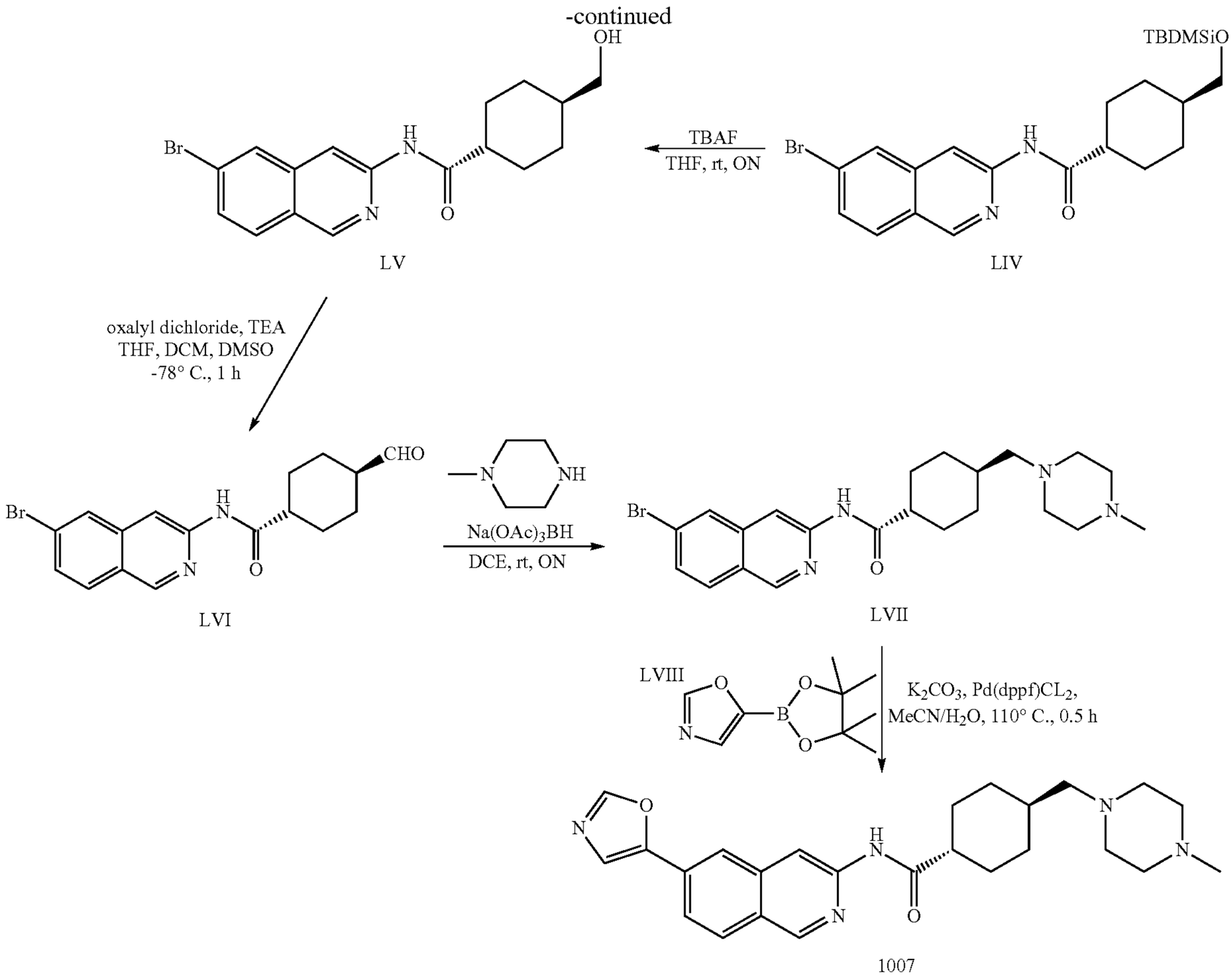


Step 1

To a mixture of methyl trans-4-(hydroxymethyl)cyclohexanecarboxylate (LI) (5.0 g, 29.03 mmol) imidazole (3.95 g, 58.07 mmol) and tert-butyl-chloro-dimethyl-silane (4.81 g, 31.94 mmol) in DMF (50 mL) was stirred at room temperature for 48 h. The solvents were concentrated to ½ volume, water (200 mL) was added and extracted with MTBE. The organic layer was separated and washed with 1 N HCl, H_2O and brine. The organics were dried over anhydrous Na_2SO_4 and the solvent was concentrated to dryness to obtain methyl trans-4-[[tert-butyl(dimethyl)silyl] oxymethyl]cyclohexanecarboxylate (LII) (8.09 g, 28.24 mmol, 97.3% yield) as a colorless oil. ESIMS found for $C_{15}H_{30}O_3Si$ m/z 287.1 (M+1).

Step 2

To a stirred solution of methyl trans-4-[[tert-butyl(dimethyl)silyl]oxymethyl]cyclohexanecarboxylate (LII) (8.05 g, 28.1 mmol) in a mixture of THF (20 mL) and MeOH (20 mL) was added 2 M solution of NaOH (28.1 mL, 56.2 mmol). The mixture was stirred at room temperature for 5 h. The solvent was reduced to ⅓ volume, acidified with 1 N HCl and the resulting solid was filtered, washed with water and dried under high vacuo to obtain 5 grams of the desired product. The filtrates were extracted with EtOAc (2×), washed with water, brine, dried over anhydrous Na_2SO_4, concentrated, and dried in vacuo to obtain another 1.1 g of trans-4-[[tert-butyl(dimethyl)silyl]oxymethyl]cyclohexanecarboxylic acid (LIII) (Total 6.1 g, 22.39 mmol, 79.7% yield) as a white solid. ^1H NMR (499 MHz, DMSO-d_6) δ ppm 0.01 (6H, s), 0.83-0.87 (8H, m), 0.88-0.96 (2H, m), 1.19-1.32 (2H, m), 1.32-1.43 (1H, m), 1.74 (2H, br dd, J=13.31, 3.16 Hz), 1.84-1.94 (2H, m), 2.09 (1H, tt, J=12.18, 3.46 Hz), 3.38 (2H, d, J=6.31 Hz), 11.98 (1H, br s); ESIMS found for $C_{14}H_{28}O_3Si$ m/z 273.1 (M+1).

Step 3

A mixture of DIPEA (5.86 mL, 33.62 mmol), DMAP (0.27 g, 2.24 mmol) and HATU (5.11 g, 13.45 mmol) in DMF (30 mL) was stirred for 10 min. 6-Bromoisoquinolin-3-amine (XII) (2.5 g, 11.21 mmol) was then added followed by the addition of trans-4-[[tert-butyl (dimethyl)silyl]oxymethyl]cyclohexanecarboxylic acid (LIII) (3.66 g, 13.45 mmol). The mixture was heated to 70° C. overnight. An additional 0.5 equiv. of HATU were added and the mixture was continued for additional 6 h. The solvent was concentrated, the residue taken up in EtOAc, washed with sat. $NaHCO_3$ and brine. The organic layer was then concentrated and the crude product was purified by column chromatography (0→30% EtOAc/hexanes). The pure fractions were combine and concentrated to obtain trans-N-(6-bromo-3-isoquinolyl)-4-[[tert-butyl(dimethyl)silyl] oxymethyl]cyclohexanecarboxamide (LIV) (2.25 g, 4.71 mmol, 42.0% yield) as a crystalline off-white solid. ^1H NMR (499 MHz, DMSO-d_6) δ ppm 0.03 (6H, s), 0.87 (9H, s), 0.98 (2H, qd, J=12.72, 3.29 Hz), 1.38-1.51 (3H, m), 1.73-1.82 (2H, m), 1.85-1.92 (2H, m), 2.46-2.55 (1H, m), 3.41 (2H, d, J=6.04 Hz), 7.62 (1H, dd, J=8.64, 1.78 Hz), 7.99 (1H, d, J=8.78 Hz), 8.16

(1H, d, J=1.65 Hz), 8.44 (1H, s), 9.13 (1H, s), 10.53 (1H, s); ESIMS found for $C_{23}H_{33}BrN_2O_2Si$ m/z 477.2 (^{79}BrM+1).

Step 4

To a stirred solution of trans-N-(6-bromo-3-isoquinolyl)-4-[[tert-butyl (dimethyl)silyl]oxymethyl]cyclohexanecarboxamide (LIV) (2.24 g, 4.69 mmol) in THF (10 mL) was added 1 M solution of TBAF (7.04 mL, 7.04 mmol) in THF. The mixture was stirred at room temperature overnight (monitored by LCMS). Water was added to the reaction mixture and extracted with EtOAc (2×). The organic layer was separated, washed with brine, and dried over anhydrous Na_2SO_4. The solvent was concentrated and the crude product was suspended in EtOAc, sonicated and the solid was collected by filtration and dried under high vacuo to obtain trans-N-(6-bromo-3-isoquinolyl)-4-(hydroxymethyl)cyclohexanecarboxamide (LV) (1.437 g, 3.96 mmol, 84.3% yield) as a light beige solid. ESIMS found for $C_{17}H_{19}BrN_2O_2$ m/z 363.1 (^{79}BrM+1).

Step 5

To a stirred solution of DMSO (0.59 mL, 8.26 mmol) in DCM (3 mL) at −78° C. was added dropwise under Ar, oxalyl dichloride (0.36 mL, 4.13 mmol) in DCM (1 mL). After 15 min, trans-N-(6-bromo-3-isoquinolyl)-4-(hydroxymethyl)cyclohexanecarboxamide (LV) (1.0 g, 2.75 mmol) in a mixture of THF (12 mL) and DMSO (0.5 mL) was added and the mixture was stirred at −78° C. for 1 h. Then, TEA (1.15 mL, 8.26 mmol) was added and the mixture was continued to stir for 1 h and warmed to room temperature for 1 h. The reaction mixture was diluted with H_2O and DCM and the organic layer separated, washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo to obtain trans-4-formyl-N-[6-(1-methylpyrazol-4-yl)-3-isoquinolyl]cyclohexanecarboxamide (LVI) (215 mg, 0.593 mmol, 108.1% yield) as a white solid which was used for next step without further purification. ESIMS found for $C_{17}H_{17}BrN_2O_2$ m/z 361.05 (^{79}BrM+1).

Step 6

To a mixture of 1-methylpiperazine (0.23 mL, 2.03 mmol), trans-N-(6-bromo-3-isoquinolyl)-4-formyl-cyclohexanecarboxamide (LVI) (490 mg, 1.36 mmol) and in DCE (6 mL) was stirred for 20 min. Then, $Na(OAc)_3BH$ (431.2 mg, 2.03 mmol) was added and the mixture was stirred overnight at room temperature. The reaction mixture was diluted with DCM, washed with sat. $NaHCO_3$, H_2O and brine. The organic layer was then separated and dried ($MgSO_4$) before concentration to dryness to obtain trans-N-(6-bromo-3-isoquinolyl)-4-[(4-methylpiperazin-1-yl) methyl]cyclohexanecarboxamide (LVII) (610 mg, 1.37 mmol, 100% yield) as a beige solid. ESIMS found for $C_{22}H_{29}BrN_4O$ m/z 445.1 (^{79}BrM+1).

Step 7

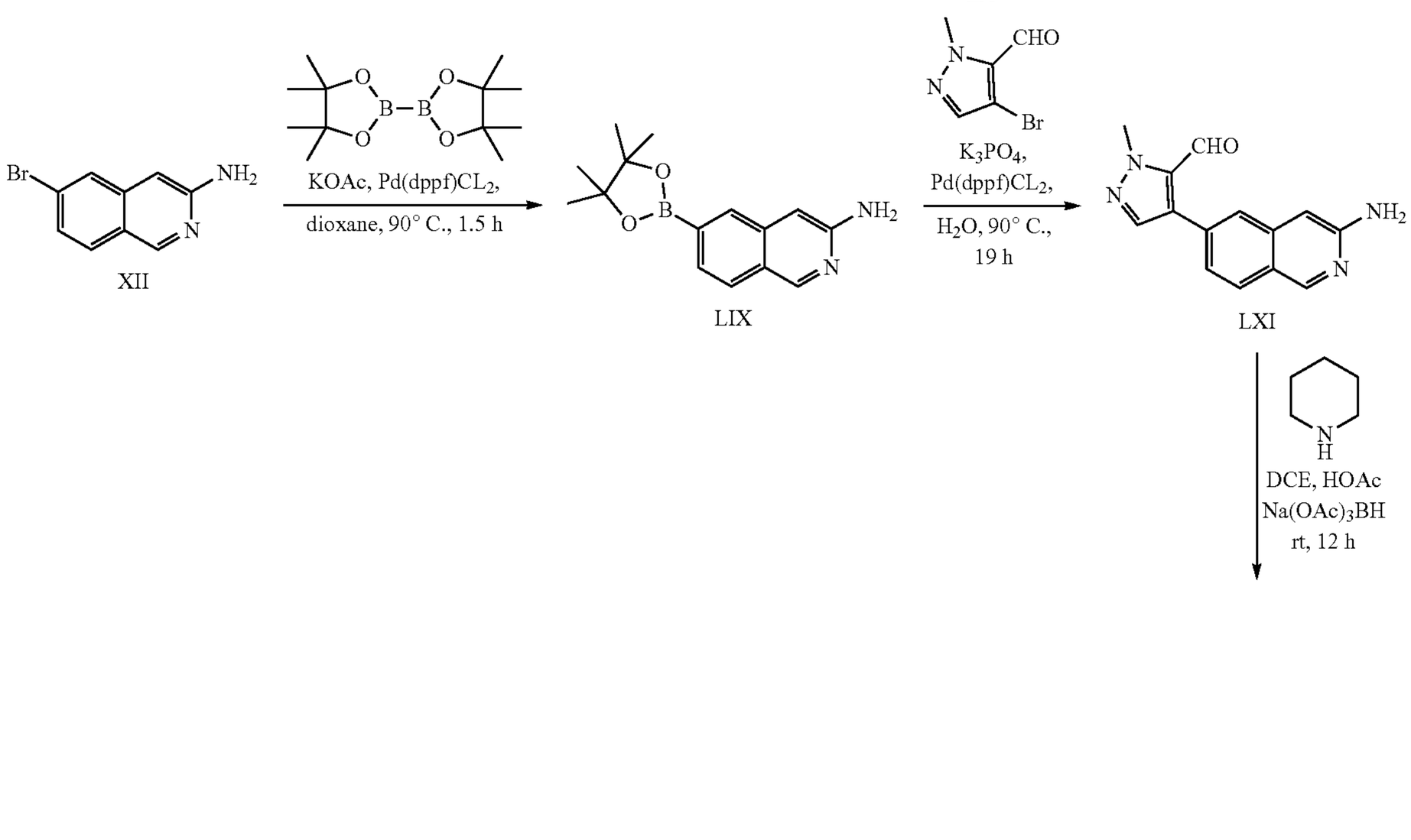
To a mixture of 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)oxazole (LVIII) (54.7 mg, 0.280 mmol), Pd(dppf)Cl_2—CH_2Cl_2 adduct (18.3 mg, 0.020 mmol), and trans-N-(6-bromo-3-isoquinolyl)-4-[(4-methylpiperazin-1-yl) methyl]cyclohexanecarboxamide (LVII) (100 mg, 0.220 mmol) was taken in MeCN (1 mL) and was added a 2 M aqueous solution of K_2CO_3 (0.28 mL, 0.560 mmol). N_2 gas was bubbled into the mixture for 10 min and then was heated to 110° C. for 0.5 h. The organic layer was separated, absorbed on silica gel and was purified by column chromatography (10→80% $CHCL_3$/10%7N NH_3 MeOH in $CHCl_3$). The pure fractions were combined, concentrated, the residue suspended in a mixture EtOAc/diethyl ether, sonicated and the resulting solid was collected by filtration and dried under vacuo to obtain trans-4-[(4-methylpiperazin-1-yl)methyl]-N-(6-oxazol-5-yl-3-isoquinolyl)cyclohexanecarboxamide (1007) (25 mg, 0.058 mmol, 25.7% yield) as a light brown solid. ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 0.83-0.96 (2H, m), 1.41-1.54 (3H, m), 1.79-1.92 (4H, m), 2.08 (2H, d, J=7.41 Hz), 2.14 (3H, s), 2.31 (8H, br s), 2.52-2.56 (1H, m), 7.86 (1H, dd, J=8.51, 1.65 Hz), 7.94 (1H, s), 8.12 (1H, d, J=8.51 Hz), 8.18 (1H, s), 8.53 (1H, s), 8.57 (1H, s), 9.12 (1H, s), 10.50 (1H, s); ESIMS found for $C_{25}H_{31}N_5O_2$ m/z 434.2 (M+1).

Example 8

Preparation of 1-isobutyl-N-(6-(1-methyl-5-(piperidin-1-ylmethyl)-1H-pyrazol-4-yl)isoquinolin-3-yl)piperidine-4-carboxamide (822) is depicted below in Scheme 18.

Scheme 18

LX



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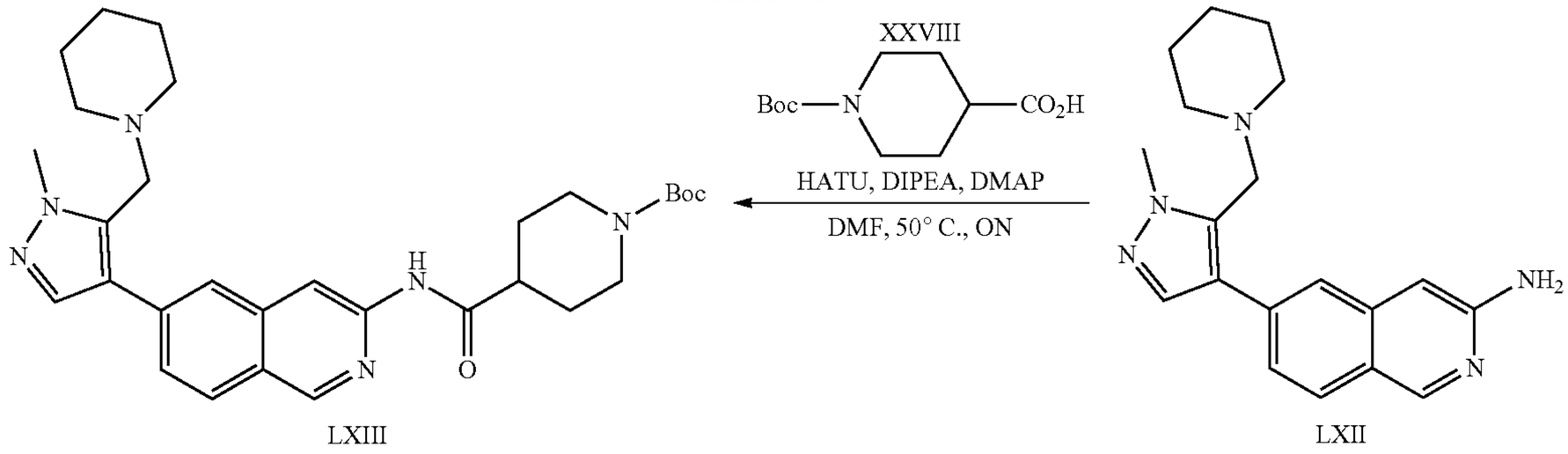


LXIV 822

Steps 1-2

To a mixture of 6-bromoisoquinolin-3-amine (XII) (4.0 g, 17.93 mmol), Pd(dppf)Cl_2—CH_2Cl_2 adduct (1.03 g, 1.26 mmol), KOAc (4.39 g, 44.83 mmol) and 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (5.01 g, 19.72 mmol) in 1,4-dioxane (50 mL) was bubbled with N_2 for 2 min. The reaction mixture was sealed and heated at 90° C. for 1.5 h. The reaction was cooled to room temperature, filtered and washed with EtOAc. The filtrate was concentrated and the residue taken in dioxane (50 mL). To the suspension was added 4-bromo-2-methyl-pyrazole-3-carbaldehyde (LX) (3.39 g, 17.93 mmol) followed by K_3PO_4 (9.52 g, 44.83 mmol), Pd(dppf)Cl_2—CH_2Cl_2 adduct (1.03 g, 1.26 mmol) and water (15 mL). The mixture was purged with N_2 for a min, sealed and heated again at 90° C. for 19 h. The mixture was cooled to room temperature and concentrated to about 20 mL. The concentrate was diluted with EtOAc and filtered through a pad of Celite. The filtrate was diluted with water and the organic layer separated. The organic layer was washed with brine; dried, filtered and concentrated. The residue was triturated in ether and the resulting solid filtered to afford 4-(3-amino-6-isoquinolyl)-2-methyl-pyrazole-3-carbaldehyde (LXI) (4.1 g, 16.2 mmol, 90.6% yield) as a brown solid. ^1H NMR (499 MHz, DMSO-d_6) δ ppm 0.01 (6H, s), 0.86 (9H, s), 0.88-1.00 (2H, m), 1.23-1.35 (2H, m), 1.35-1.46 (1H, m), 1.69-1.79 (2H, m), 1.85-1.95 (2H, m), 2.21 (1H, tt, J=12.21, 3.57 Hz), 3.38 (2H, d, J=6.31 Hz), 3.57 (3H, s) ESIMS found for $C_{14}H_{12}N_4O$ m/z 252.95 (M+1).

Step 3

To a mixture of 4-(3-amino-6-isoquinolyl)-2-methyl-pyrazole-3-carbaldehyde (LXI) (1.07 g, 4.25 mmol), piperidine (0.84 mL, 8.51 mmol) and catalytic HOAc in DCE (10 mL) was stirred for 30 min. $Na(OAc)_3BH$ (1.8 g, 8.51 mmol) was added and stirring was continued for 12 h at room temperature. The reaction mixture was quenched with minimum amount of aq. saturated ammonium chloride solution, and concentrated under vacuum. The residue was adsorbed on silica gel and purified by chromatography (0→20% 7N NH_3-MeOH/$CHCl_3$) to obtain 6-[1-methyl-5-(1-piperidylmethyl)pyrazol-4-yl]isoquinolin-3-amine (LXII) (800 mg, 2.49 mmol, 58.5% yield) as a white solid. ESIMS found for $C_{19}H_{23}N_5$ m/z 322.2 (M+1).

Step 4

To a mixture of 1-tert-butoxycarbonylpiperidine-4-carboxylic acid (XXVIII) (1.15 mL, 1.63 mmol), HATU (703.87 mg, 1.85 mmol) and DIPEA (0.57 mL, 3.27 mmol) in DMF (5 mL) was stirred for 10 min. To this mixture was added 6-[1-methyl-5-(1-piperidylmethyl) pyrazol-4-yl]isoquinolin-3-amine (LXII) (350 mg, 1.09 mmol) and DMAP (26.61 mg, 0.220 mmol) and the mixture was stirred at 50° C. overnight. The solvent was concentrated and the residue was taken up in EtOAc, washed with sat. $NaHCO_3$, water and brine. The organic layer was then separated and dried ($MgSO_4$) before concentrating to dryness. The crude product was purified by column chromatography (25%→100% EtOAc/hexanes). The pure fractions were combined, concentrated, the residue triturated with diethyl ether, sonicated and the solid were collected by filtration and dried under high vacuo to obtain tert-butyl 4-[[6-[1-methyl-5-(1-piperidylmethyl) pyrazol-4-yl]-3-isoquinolyl]carbamoyl]piperidine-1-carboxylate (LXIII) (550 mg, 1.03 mmol, 94.8% yield) as a dark beige solid. ESIMS found for $C_{30}H_{40}N_6O_3$ m/z 533.3 (M+1).

Step 5

To a stirred solution of tert-butyl 4-[[6-[1-methyl-5-(1-piperidylmethyl) pyrazol-4-yl]-3-isoquinolyl]carbamoyl]piperidine-1-carboxylate (LXIII) (300 mg, 0.560 mmol) in DCM (5 mL) was added TFA (1.23 mL, 15.91 mmol). The mixture was stirred overnight at room temperature. The solvent was evaporated and the residue was adsorbed on silica gel, purified by column chromatography (0-10% 7N.NH_4-MeOH/$CHCl_3$), pure fractions were concentrated and the solid were triturated with MeOH, filtered and dried to obtain N-[6-[1-methyl-5-(1-piperidylmethyl) pyrazol-4-yl]-3-isoquinolyl]piperidine-4-carboxamide (LXIV) (191 mg, 0.441 mmol, 78.4% yield) as a white solid. ESIMS found for $C_{25}H_{32}N_6O$ m/z 433.3 (M+1).

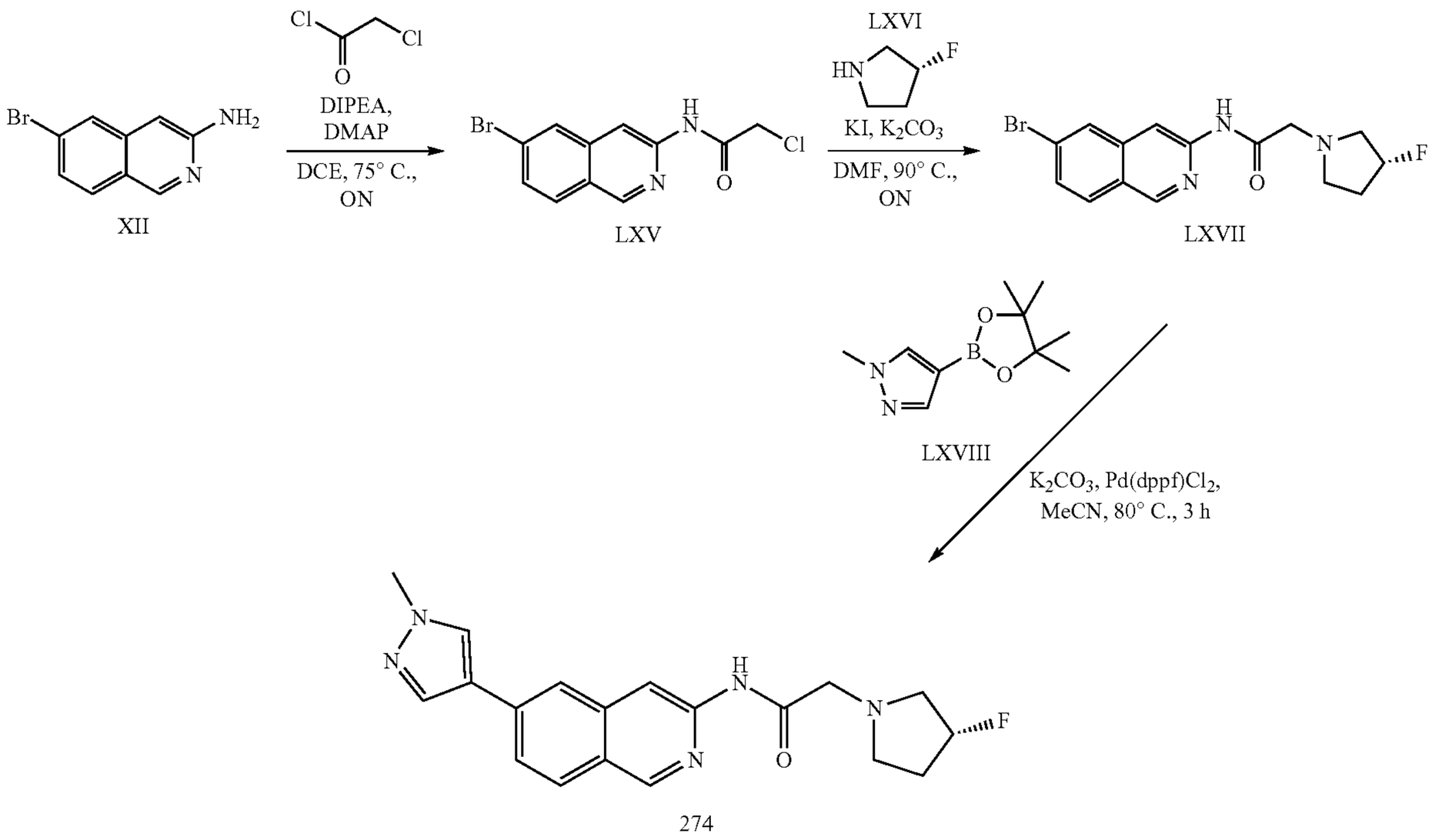
Step 6

To stirred mixture of N-[6-[1-methyl-5-(1-piperidylmethyl)pyrazol-4-yl]-3-isoquinolyl]piperidine-4-carboxamide (LXIV) (95 mg, 0.220 mmol) and 2-methylpropanal (0.06 mL, 0.660 mmol) in MeOH (2 mL) was added $NaCNBH_3$ (27.6 mg, 0.440 mmol) at 0° C. The mixture was stirred for 30 min→1 h at room temperature. Reaction mixture was quenched with minimum amount of aq. saturated ammonium chloride solution, concentrated under vacuum and the residue was adsorbed on silica gel, purified by chromatography (0→10% 7N.NH3-MeOH/$CHCl_3$) to obtain 1-isobutyl-N-[6-[1-methyl-5-(1-piperidylmethyl)pyrazol-4-yl]-3-isoquinolyl]piperidine-4-carboxamide (822) (30 mg, 0.061 mmol, 28.0% yield) as a beige solid. ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 0.86 (6H, d, J=6.59 Hz), 1.33-1.42 (2H, m), 1.45-1.53 (4H, m), 1.61-1.72 (2H, m), 1.72-1.81 (3H, m), 1.86 (2H, td, J=11.60, 1.78 Hz), 2.02 (2H, d, J=7.41 Hz), 2.36 (4H, br s), 2.52-2.59 (1H, m), 2.86 (2H, br d, J=11.53 Hz), 3.65 (2H, s), 3.91 (3H, s), 7.68 (1H, dd, J=8.37, 1.51 Hz), 7.79 (1H, s), 8.02 (1H, d, J=9.33 Hz), 8.03 (1H, s), 8.46 (1H, s), 9.07 (1H, s), 10.46 (1H, s); ESIMS found for $C_{29}H_{40}N_6O$ m/z 489.3 (M+1).

Example 9

Preparation of 2-[(3R)-3-fluoropyrrolidin-1-yl]-N-[6-(1-methylpyrazol-4-yl)-3-isoquinolyl]acetamide (274) is depicted below in Scheme 19.

Scheme 19



Step 1

To a stirred suspension of 6-bromoisoquinolin-3-amine (XII) (1.0 g, 4.48 mmol) and DMAP (109.5 mg, 0.90 mmol) in DCE (35 mL) was added DIPEA (3.12 mL, 17.93 mmol) followed by the addition of 2-chloroacetyl chloride (1.07 mL, 13.45 mmol). The mixture was heated to 75° C. overnight. The reaction mixture was then cooled to room temperature, diluted with DCM, washed with H_2O and brine, the organic layer were then separated and dried over $MgSO_4$ before concentrating to dryness. The crude product was then purified by flash column chromatography using EtOAc/hexanes (0→100%) to obtain N-(6-bromo-3-isoquinolyl)-2-chloro-acetamide (LXV) as a light yellow solid (350 mg, 1.16 mmol, 26.1% yield). ESIMS found for $C_{11}H_8BrClN_2O$ m/z 298.9 (^{79}BrM+H).

Step 2

To a solution of N-(6-bromo-3-isoquinolyl)-2-chloro-acetamide (LXV) (100 mg, 0.33 mmol), (3R)-3-fluoropyrrolidine hydrochloride (LXVI) (209.6 mg, 1.67 mmol), KI (0.02 mL, 0.33 mmol) and K_2CO_3 (461.4 mg, 3.34 mmol) in DMF (2 mL) was heated to 90° C. overnight. The reaction was then concentrated to dryness and the residue was taken up in EtOAc and the organic layer was washed with water then brine. The organic layer was then separated and dried over $MgSO_4$ before concentration to dryness to obtain N-(6-bromo-3-isoquinolyl)-2-[(3R)-3-fluoropyrrolidin-1-yl]acetamide (LXVII) as a dark brown thick gum (110 mg, 0.312

mmol, 94.6% yield). Used for next step without purification. ESIMS found for $C_{15}H_{15}BrFN_3O$ m/z 352.2 (^{79}BrM+H).

Step 3

To a solution of N-(6-bromo-3-isoquinolyl)-2-[(3R)-3-fluoropyrrolidin-1-yl]acetamide (LXVII) (116.2 mg, 0.33 mmol), 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazolo (LXVIII) (103 mg, 0.50 mmol), Pd(dppf)Cl_2 (27 mg, 0.03 mmol) in MeCN (1.5 mL) was added a 2 M aqueous solution of K_2CO_3 (0.5 mL, 0.99 mmol). N_2 gas was bubbled into the mixture for 10 min and then heated to 80° C. for 3 h. The organic layer was carefully separated, absorbed on silica gel and purified by flash column chromatography (0→30% $CHCl_3$/10% 7 N NH_3 in MeOH). The pure fractions were concentrated, the residue suspended in minimum EtOAc, sonicated and the resulting solid was collected by filtration, washed with diethyl ether and dried to obtain 2-[(3R)-3-fluoropyrrolidin-1-yl]-N-[6-(1-methyl-pyrazol-4-yl)-3-isoquinolyl]acetamide (274) as a white solid (58.0 mg, 0.164 mmol, 49.7% yield). ^{1}H NMR (DMSO-d_6, 500 MHz) δ ppm 1.88-2.03 (m, 1H), 2.12-2.28 (m, 1H), 2.53-2.61 (m, 1H), 2.86 (ddd, J=32.40, 11.80, 4.95 Hz, 1H), 2.95-3.04 (m, 2H), 3.41 (s, 2H), 3.90 (s, 3H), 5.26 (ddd, J=55.80, 6.05, 4.95 Hz, 1H), 7.77 (dd, J=8.51, 1.37 Hz, 1H), 8.02 (d, J=8.78 Hz, 1H), 8.10 (s, 2H), 8.37 (s, 1H), 8.44 (s, 1H), 9.03 (s, 1H), 10.02 (s, 1H); ESIMS found for $C_{19}H_{20}FN_5O$ m/z 354.1 (M+1).

Example 10

Preparation of (S)—N-(6-(1-(methyl-d_3)-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(pyrrolidin-1-yl)propanamide (971) is depicted below in Scheme 20.

Step 1

To a stirred suspension of 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (LXIX) (1.435 g, 7.4 mmol) and Cs_2CO_3 (2.89 g, 8.87 mmol) in DMF (15 mL) was added trideuterio(iodo)methane (0.51 mL, 8.13 mmol) and the mixture was stirred at room temperature overnight. The reaction mixture was filtered and the filtrates were concentrated and dried under high vacuo to obtain 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(trideuteriomethyl)pyrazole (LXX) (3.9 g, 18.48 mmol, 249.8% yield) as a white solid which was used for next step without purification. ESIMS found for $C_{10}H_{14}[^2H_3]BN_2O_2$ m/z 212. (M+1).

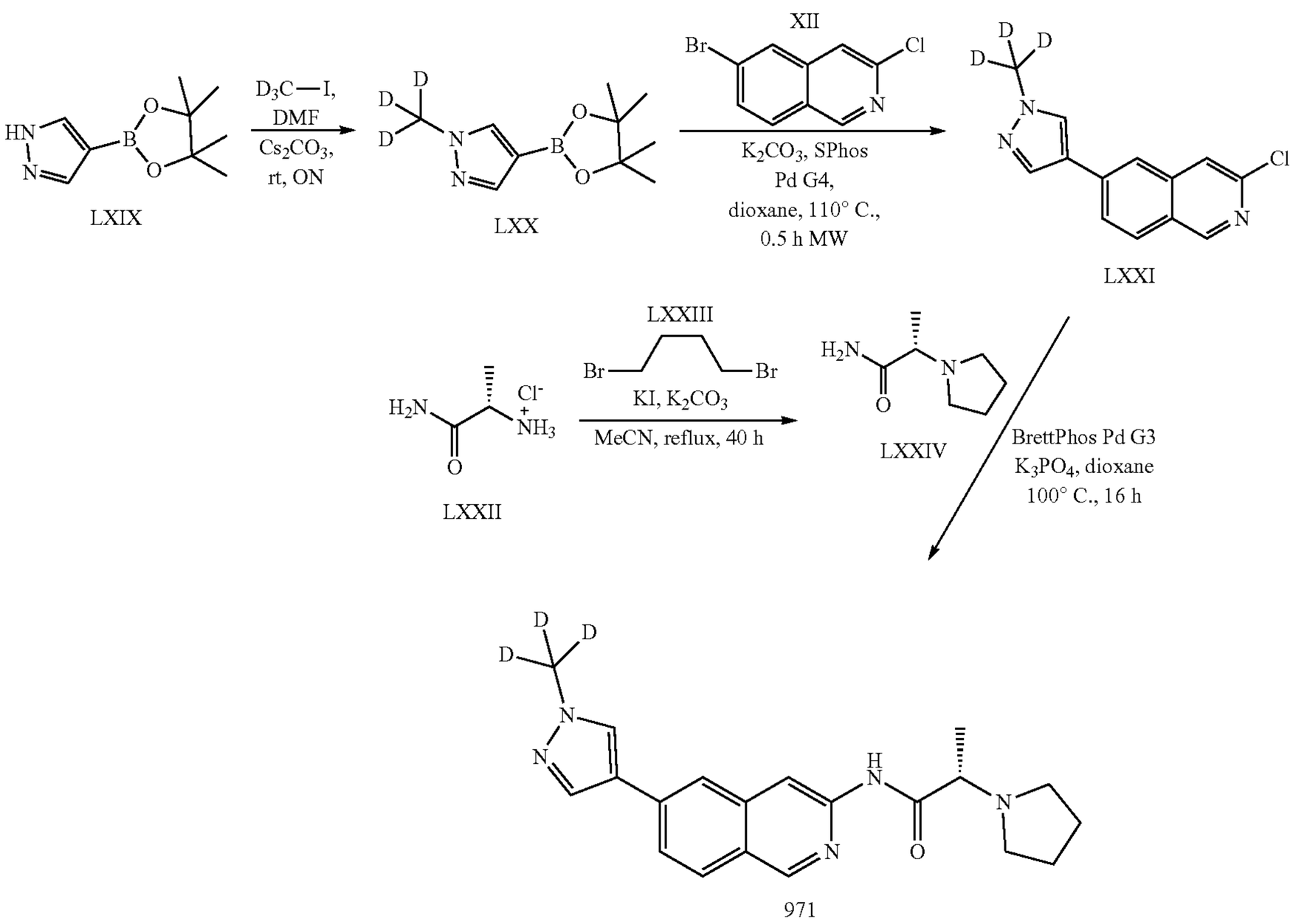
Step 2

To a mixture of 6-bromo-3-chloro-isoquinoline (XII) (0.5 g, 2.06 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(trideuteriomethyl)pyrazole (LXX) (1.305 g, 6.19 mmol) and SPhos Pd G4 (81.9 mg, 0.100 mmol) in 1,4-dioxane (10 mL) and was added a 2 M aqueous solution of K_2CO_3 (3.88 mL, 7.77 mmol). N_2 gas was bubbled into the mixture for 10 min and then the mixture was heated to 110° C. for 0.5 h in a microwave. The organic layer was carefully separated, absorbed on silica gel and purified by column chromatography (0→100% hexanes/EtOAc) to obtain 3-chloro-6-[1-(trideuteriomethyl)pyrazol-4-yl]isoquinoline (LXXI) (400 mg, 1.62 mmol, 78.6% yield) as an off-white solid. ESIMS found for $C_{13}H_7[^2H_3]ClN_3$ m/z 246.9 (M+1).

Step 3

To a mixture of (S)-2-aminopropanamide HCl (LXXII) (100 mg, 0.330 mmol), 1,4-dibromobutane (LXXIII) (1.9 mL, 16.06 mmol), K_2CO_3 (4.437 g, 32.11 mmol) and KI

Scheme 20



(266.5 mg, 1.61 mmol) in MeCN (80 mL) was heated to reflux for 40 h. 1 N hydrochloric acid (100 mL) and DCM (100 mL) were added to the reaction mixture. The organic phase is separated off and discarded. The aqueous phase is made basic with a NaOH solution and extracted with $CHCl_3$ (3×80 ml). The organic layers were combined and dried under high vacuo to obtain (2S)-2-pyrrolidin-1-ylpropanamide (LXXIV) (1.10 g, 7.45 mmol, 46.4% yield) as a white solid which was used for next step without purification. ^1H NMR (499 MHz, DMSO-d_6) δ ppm 1.15 (3H, d, J=6.86 Hz), 1.63-1.72 (4H, m), 2.44-2.49 (4H, m), 2.72 (1H, q, J=6.68 Hz), 6.88 (1H, br s), 7.07 (1H, br s) ESIMS found for $C_7H_{14}N_2O$ m/z 143.1 (M+1).

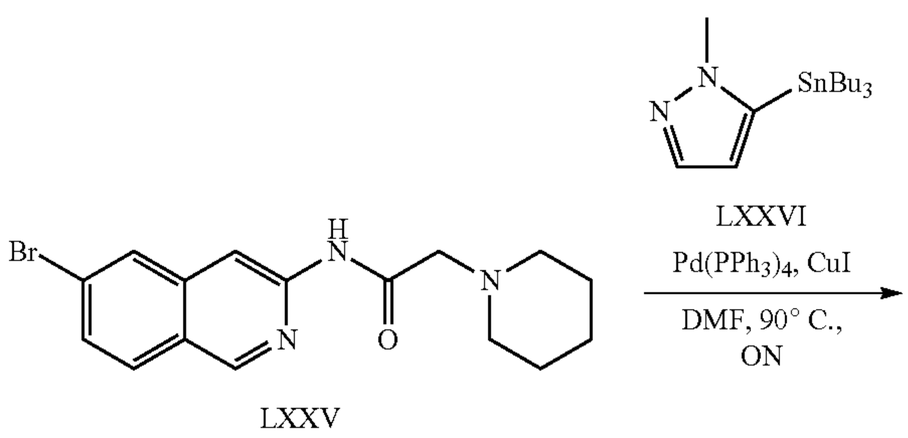
Step 4

To a mixture of (2S)-2-pyrrolidin-1-ylpropanamide (LXXIV) (420.1 mg, 2.95 mmol) BrettPhos Pd G3 (223.2 mg, 0.250 mmol), 3-chloro-6-[1-(trideuteriomethyl)pyrazol-4-yl]isoquinoline (LXXI) (200 mg, 0.810 mmol) and K_3PO_4 (1.045 g, 4.92 mmol) was taken in 1,4-dioxane (5 mL). N_2 gas was bubbled into the mixture for 10 min and then the mixture was heated to 100° C. for 16 h. The reaction mixture was filtered through Celite, washed with EtOAc, the filtrates concentrated and the crude product was purified by flash chromatography followed by preparative TLC (50% $CHCl_3$/10% 7N NH_3 in MeOH) to obtain (2S)-2-pyrrolidin-1-yl-N-[6-[1-(trideuteriomethyl)pyrazol-4-yl]-3-isoquinolyl]propanamide (971) (150.0 mg, 0.426 mmol, 50.6% yield) as a beige solid. ^1H NMR (499 MHz, DMSO-d_6) δ ppm 1.30 (3H, d, J=6.86 Hz), 1.75 (4H, br s), 2.59-2.69 (4H, m), 3.29-3.32 (1H, m), 7.76 (1H, dd, J=8.51, 1.65 Hz), 8.02 (1H, d, J=8.51 Hz), 8.08 (2H, s), 8.35 (1H, s), 8.43 (1H, s), 9.03 (1H, s), 9.91 (1H, s); ESIMS found for $C_{20}H_{20}[^2H_3]N_5O$ m/z 353.0 (M+1).

Example 11

Preparation of N-[6-(3-methylimidazol-4-yl)-3-isoquinolyl]-2-(1-piperidyl) acetamide (275) is depicted below in Scheme 21.

Scheme 21



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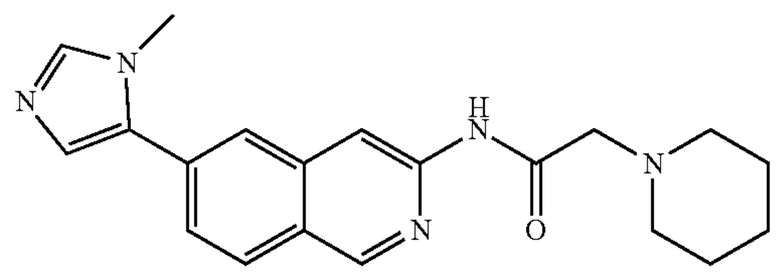


275

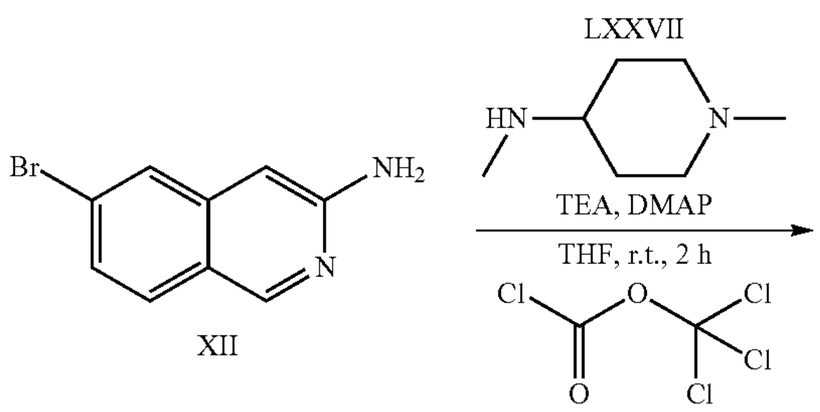
Step 1

To a stirred mixture of N-(6-bromo-3-isoquinolyl)-2-(1-piperidyl)acetamide (LXXV) (100 mg, 0.29 mmol) tributyl-(3-methylimidazol-4-yl)stannane (LXXVI) (117.24 mg, 0.32 mmol) $Pd(PPh_3)_4$ (33.2 mg, 0.03 mmol) and cuprous iodide (5.47 mg, 0.03 mmol) in DMF (2 mL) was bubbled N_2 gas for 10 min and then heated to 90° C. overnight. The reaction mixture was concentrated, absorbed on silica gel and purified by flash column chromatography using $CHCl_3$/10% 7 N NH_3 in MeOH (0→40%). The pure fractions were concentrated, the residue suspended in diethyl ether, sonicated and the resulting solids were collected by filtration, and dried to obtain N-[6-(3-methylimidazol-4-yl)-3-isoquinolyl]-2-(1-piperidyl)acetamide (275) as a white solid (53.0 mg, 0.152 mmol, 52.3% yield). ^1H NMR (DMSO-d_6, 500 MHz) δ ppm 1.43 (br d, J=4.94 Hz, 2H), 1.59 (quin, J=5.63 Hz, 4H), 2.52 (br d, J=5.21 Hz, 4H), 3.18 (s, 2H), 3.84 (s, 3H), 7.33 (br s, 1H), 7.70 (dd, J=8.51, 1.65 Hz, 1H), 7.81 (br s, 1H), 8.06 (s, 1H), 8.11 (d, J=8.51 Hz, 1H), 8.53 (s, 1H), 9.14 (s, 1H), 9.98 (s, 1H); ESIMS found for $C_{20}H_{23}N_5O$ m/z 350.2 (M+1).

Example 12

Preparation of 1-methyl-3-(6-(1-methyl-1H-pyrazol-4-yl) isoquinolin-3-yl)-1-(1-methylpiperidin-4-yl)urea (1037) is depicted below in Scheme 22.

Scheme 22



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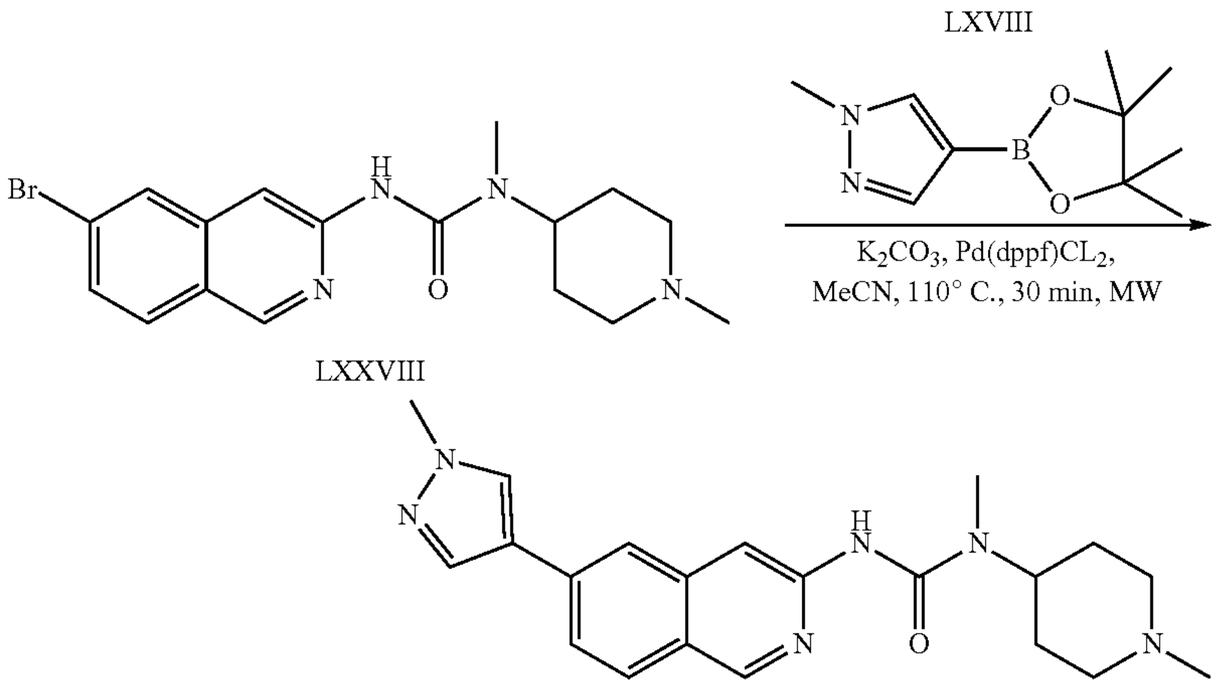


Step 1

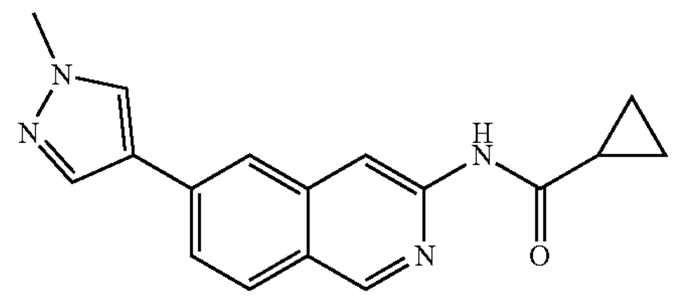
To a stirred suspension of 6-bromoisoquinolin-3-amine (XII) (200 mg, 0.900 mmol), DMAP (11 mg, 0.090 mmol) and TEA (0.5 mL, 3.59 mmol) in THF (40 ml) was added trichloromethyl carbonochloridate (0.11 mL, 0.900 mmol) and the mixture was stirred for 1 h at room temperature. N,1-dimethylpiperidin-4-amine (LXXVII) (115 mg, 0.900 mmol) was then added and the mixture was stirred for 2 h at room temperature. The reaction was concentrated and the residue taken in DCM, washed with water, sat. $NaHCO_3$ and brine. The organic layer was dried over anhydrous Na_2SO_4, solvents removed in vacuo and the crude was purified by column chromatography (0→10% $CHCl_3$/7N NH_3 in MeOH) to obtain 3-(6-bromo-3-isoquinolyl)-1-methyl-1-(1-methyl-4-piperidyl)urea (LXXVIII) (98 mg, 0.260 mmol, 29.0% yield) as a beige solid. ESIMS found for $C_{17}H_{21}BrN_4O$ m/z 377.1 (^{79}BrM+H).

Step 2

To a mixture of $Pd(dppf)Cl_2$—CH_2Cl_2 adduct (19.6 mg, 0.020 mmol), 1-(6-bromo-3-isoquinolyl)-3-(1-methyl-4-piperidyl)urea (LXXVIII) (87 mg, 0.240 mmol), and 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) pyrazole (LXVIII) (59.8 mg, 0.290 mmol) in MeCN (5 mL) was added a 2 M aqueous solution of K_2CO_3 (0.24 mL, 0.480 mmol). N_2 gas was bubbled into the mixture for 10 min and then heated at 110° C. for 30 min in a microwave. The organic layer was carefully separated, absorbed on silica gel and purified by flash column chromatography (0→10% 7N NH_3 in MeOH/$CHCl_3$). The pure fractions were combined, concentrated and the residue was triturated from DCM/hexanes. The solid was collected by filtration and dried under high vacuum to obtain 1-(1-methyl-4-piperidyl)-3-[6-(1-methylpyrazol-4-yl)-3-isoquinolyl]urea (1037) (35 mg, 0.096 mmol, 40.1% yield) as a beige solid. ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.52 (2H, br d, J=10.15 Hz), 1.74 (2H, qd, J=12.12, 3.70 Hz), 1.93-2.02 (2H, m), 2.17 (3H, s), 2.82 (2H, br d, J=11.25 Hz), 2.88 (3H, s), 3.90 (3H, s), 4.09 (1H, tt, J=12.01, 3.91 Hz), 7.65-7.72 (1H, m), 7.93-7.99 (2H, m), 8.06 (1H, s), 8.15 (1H, s), 8.33 (1H, s), 8.76 (1H, s), 8.97 (1H, s); ESIMS found for $C_{21}H_{26}N_6O$ m/z 379.2 (M+1).

The following compounds were prepared in accordance with the procedures described in the above Examples 1-12.

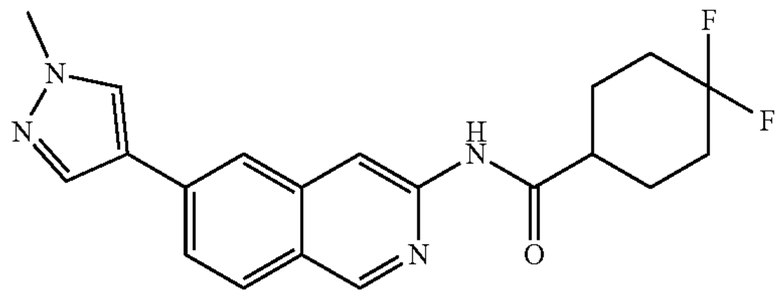
1



N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl) cyclopropanecarboxamide 1

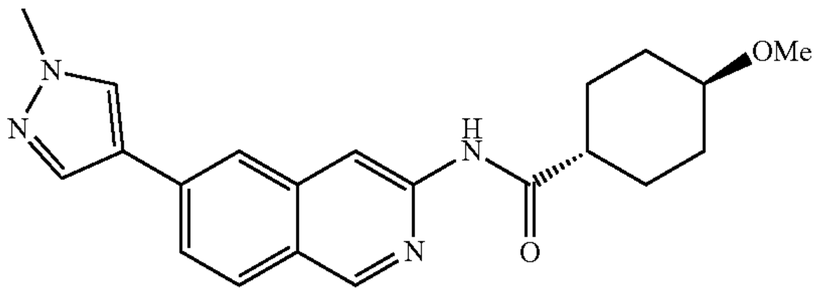
Beige solid (32.0 mg, 0.109 mmol, 31.9% yield). ^{1}H NMR (DMSO-d_6, 500 MHz) δ ppm 0.77-0.90 (m, 4H), 2.03-2.12 (m, 1H), 3.90 (s, 3H), 7.74 (dd, J=8.51, 1.65 Hz, 1H), 7.96-8.03 (m, 2H), 8.08 (s, 1H), 8.35 (s, 1H), 8.40 (s, 1H), 9.03 (s, 1H), 10.83 (s, 1H); ESIMS found for $C_{17}H_{16}N_4O$ m/z 293.1 (M+1).

3



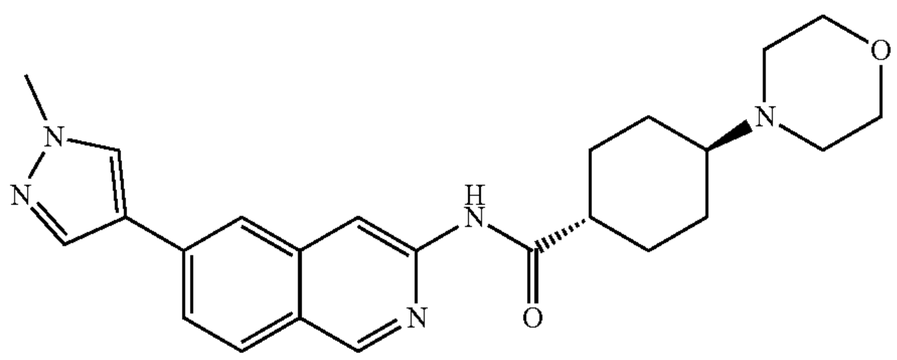
4,4-Difluoro-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl) cyclohexanecarboxamide 3

Beige solid (41.6 mg, 0.112 mmol, 56.2% yield). ^{1}H NMR (DMSO-d_6, 500 MHz) δ ppm 1.66-1.90 (m, 4H), 1.91-2.00 (m, 2H), 2.06-2.18 (m, 2H), 2.66-2.76 (m, 1H), 3.90 (s, 3H), 7.75 (dd, J=8.64, 1.51 Hz, 1H), 8.00 (d, J=8.51 Hz, 1H), 8.04 (s, 1H), 8.08 (s, 1H), 8.35 (s, 1H), 8.43 (s, 1H), 9.03 (s, 1H), 10.57 (s, 1H); ESIMS found for $C_{20}H_{20}F_2N_4O$ m/z 371.2 (M+1).



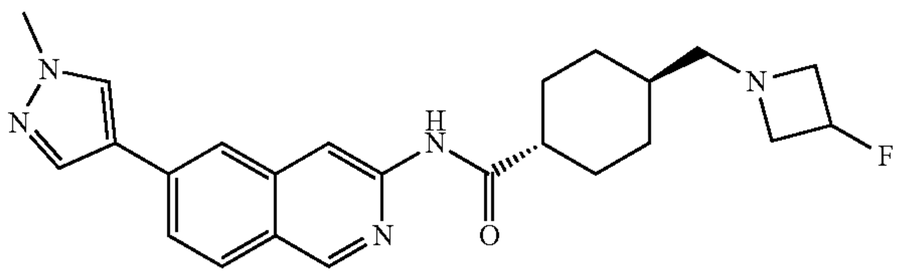
trans-4-Methoxy-N-(6-(1-methyl-1H-pyrazol-4-yl) isoquinolin-3-yl) cyclohexane-1-carboxamide 4

White solid (101 mg, 0.277 mmol, 62.2% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.07-1.17 (2H, m), 1.43-1.56 (2H, m), 1.84-1.95 (2H, m), 2.03-2.11 (2H, m), 2.51-2.57 (1H, m), 3.12 (1H, tt, J=10.67, 4.15 Hz), 3.25 (3H, s), 3.90 (3H, s), 7.74 (1H, dd, J=8.51, 1.65 Hz), 7.99 (1H, d, J=8.51 Hz), 8.02 (1H, s), 8.07 (1H, s), 8.34 (1H, s), 8.42 (1H, s), 9.02 (1H, s), 10.42 (1H, s); ESIMS found for $C_{21}H_{24}N_4O_2$ m/z 365.2 (M+1).



trans-N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-4-morpholinocyclohexane-1-carboxamide 6

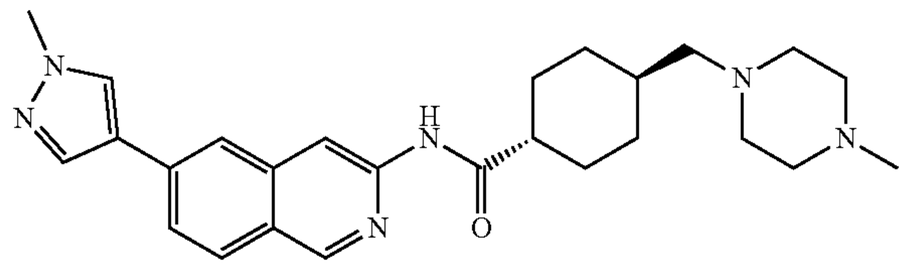
White solid (36 mg, 0.086 mmol, 30.0% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.15-1.30 (2H, m), 1.41-1.56 (2H, m), 1.91 (4H, br t, J=11.11 Hz), 2.17-2.28 (1H, m), 3.28 (4H, br s), 3.50-3.60 (4H, m), 3.90 (3H, s), 7.74 (1H, dd, J=8.51, 1.65 Hz), 7.99 (1H, d, J=8.51 Hz), 8.02 (1H, s), 8.07 (1H, s), 8.35 (1H, s), 8.42 (1H, s), 9.02 (1H, s), 10.41 (1H, s); ESIMS found for $C_{24}H_{29}N_5O_2$ m/z 420.2 (M+1).



trans-4-((3-Fluoroazetidin-1-yl)methyl)-N-(6-(1-methyl-1H-pyrazol-4-yl) isoquinolin-3-yl)cyclohexane-1-carboxamide 10

White solid (42.0 mg, 0.100 mmol, 36.1% yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 0.91 (2H, qd, J=12.67, 3.16 Hz), 1.20-1.33 (1H, m), 1.37-1.51 (2H, m), 1.51-1.61 (1H, m), 1.75-1.90 (4H, m), 2.29 (2H, d, J=6.86 Hz), 2.96-3.08 (2H, m), 3.48-3.60 (2H, m), 3.90 (3H, s), 5.02-5.22 (1H, m), 7.73 (1H, dd, J=8.51, 1.65 Hz), 7.99 (1H, d, J=8.51 Hz), 8.02 (1H, s), 8.07 (1H, s), 8.34 (1H, s), 8.42 (1H, s), 9.01 (1H, s), 10.38 (1H, s); ESIMS found for $C_{24}H_{28}FN_5O$ m/z 422.0 (M+1).

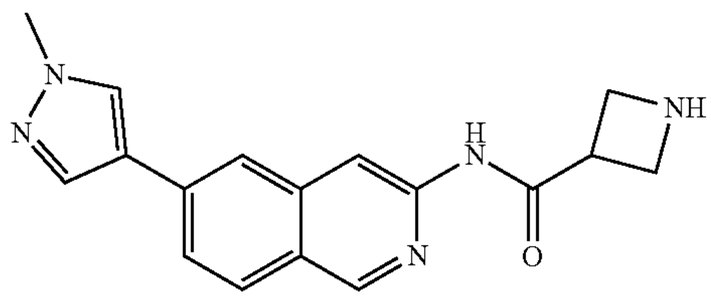
14



trans-N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-4-((4-methylpiperazin-1-yl)methyl)cyclohexane-1-carboxamide 14

White solid (35.0 mg, 0.078 mmol, 28.4% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 0.82-0.95 (2H, m), 1.40-1.54 (4H, m), 1.79-1.91 (4H, m), 2.08 (2H, d, J=7.14 Hz), 2.14 (3H, s), 2.23-2.41 (8H, m), 3.90 (3H, s), 7.73 (1H, dd, J=8.51, 1.37 Hz), 7.99 (1H, d, J=8.51 Hz), 8.02 (1H, s), 8.07 (1H, s), 8.34 (1H, s), 8.43 (1H, s), 9.01 (1H, s), 10.37 (1H, s); ESIMS found for $C_{26}H_{34}N_6O$ m/z 447.0 (M+1).

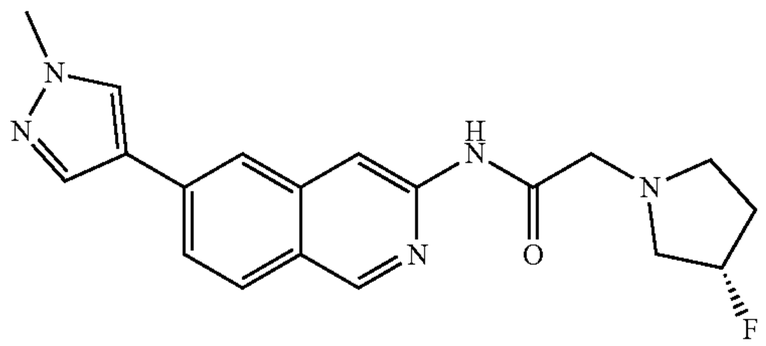
16



N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl) azetidine-3-carboxamide 16

Yellow solid (10.8 mg, 0.035 mmol, 62.4% yield). ^{1}H NMR (DMSO-d_6, 500 MHz) δ ppm 3.50 (br s, 2H), 3.76 (br s, 3H), 3.90 (s, 3H), 7.75 (dd, J=8.51, 1.37 Hz, 1H), 8.00 (d, J=8.51 Hz, 1H), 8.06 (s, 1H), 8.09 (s, 1H), 8.36 (s, 1H), 8.47 (s, 1H), 9.02 (s, 1H), 10.45 (s, 1H); ESIMS found for $C_{17}H_{17}N_5O$ m/z 308.1 (M+1).

69

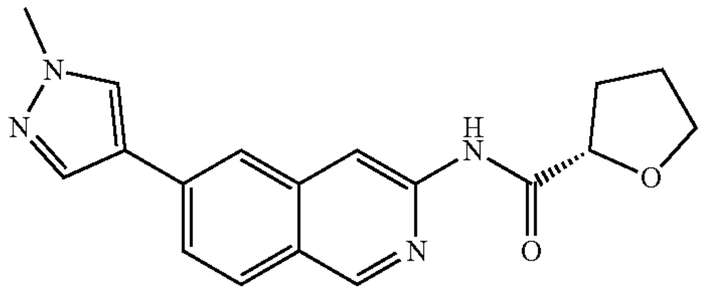


(S)-2-(3-Fluoropyrrolidin-1-yl)-N-(6-(1-methyl-1H-pyrazol-4-yl) isoquinolin-3-yl)acetamide 69

Off-white solid (70.0 mg, 0.198 mmol, 41.0% yield). ^{1}H NMR (DMSO-d_6, 500 MHz) δ ppm 1.87-2.04 (m, 1H),

2.12-2.29 (m, 1H), 2.55-2.62 (m, 1H), 2.81-2.94 (m, 1H), 2.96-3.06 (m, 2H), 3.42 (s, 2H), 5.17-5.35 (m, 1H), 7.77 (dd, J=8.64, 1.51 Hz, 1H), 8.02 (d, J=8.78 Hz, 1H), 8.10 (d, J=0.82 Hz, 2H), 8.36 (s, 1H), 8.44 (s, 1H), 9.03 (s, 1H), 10.02 (s, 1H); ESIMS found for $C_{19}H_{20}FN_5O$ m/z 354.2 (M+1).

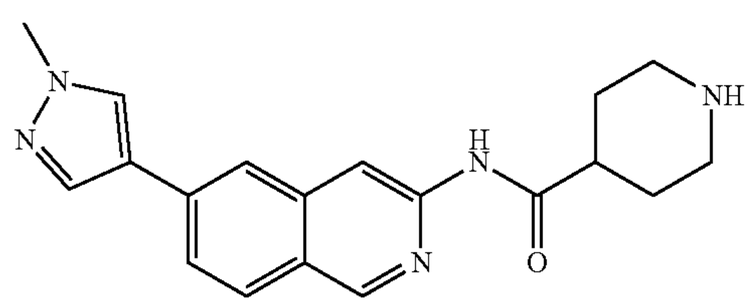
71



(S)—N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)tetrahydrofuran-2-carboxamide 71

Off-white solid (30.0 mg, 0.093 mmol, 59.8% yield). ^{1}H NMR (DMSO-d_6, 500 MHz) δ ppm 1.83-1.96 (m, 2H), 1.97-2.07 (m, 1H), 2.19-2.30 (m, 1H), 3.83-3.88 (m, 1H), 3.90 (s, 3H), 3.99-4.07 (m, 1H), 4.53 (dd, J=8.23, 5.76 Hz, 1H), 7.78 (dd, J=8.51, 1.65 Hz, 1H), 8.03 (d, J=8.51 Hz, 1H), 8.10 (s, 2H), 8.37 (s, 1H), 8.42 (s, 1H), 9.05 (s, 1H), 9.75 (s, 1H); ESIMS found for $C_{18}H_{18}N_4O_2$ m/z 323.2 (M+1).

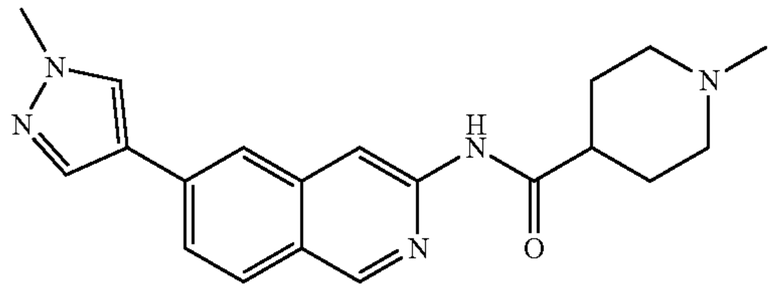
72



N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)piperidine-4-carboxamide 72

White solid (75.0 mg, 0.224 mmol, 92.2% yield). ^{1}H NMR (DMSO-d_6, 500 MHz) δ ppm 1.65 (qd, J=12.30, 3.70 Hz, 2H), 1.81 (br d, J=10.70 Hz, 2H), 2.64 (td, J=12.28, 2.33 Hz, 2H), 2.71 (ddt, J=11.32, 7.62, 3.84, 3.84 Hz, 1H), 3.12 (br d, J=12.35 Hz, 2H), 3.90 (s, 3H), 7.75 (dd, J=8.51, 1.37 Hz, 1H), 8.00 (d, J=8.51 Hz, 1H), 8.04 (s, 1H), 8.08 (s, 1H), 8.35 (s, 1H), 8.43 (s, 1H), 9.03 (s, 1H), 10.50 (s, 1H); ESIMS found for $C_{19}H_{21}N_5O$ m/z 336.1 (M+1).

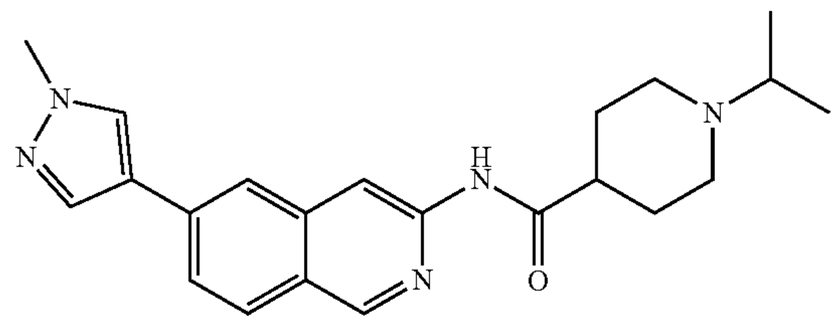
73



1-Methyl-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)piperidine-4-carboxamide 73

White solid (114.0 mg, 0.326 mmol, 42.1% yield). ^{1}H NMR (DMSO-d_6, 500 MHz) δ ppm 1.60-1.73 (m, 2H), 1.73-1.80 (m, 2H), 1.86 (td, J=11.66, 2.20 Hz, 2H), 2.16 (s, 3H), 2.45-2.55 (m, 1H), 2.81 (br d, J=11.53 Hz, 2H), 3.90 (s, 3H), 7.74 (dd, J=8.51, 1.65 Hz, 1H), 8.00 (d, J=8.51 Hz, 1H), 8.02 (s, 1H), 8.07 (s, 1H), 8.35 (s, 1H), 8.43 (s, 1H), 9.02 (s, 1H), 10.46 (s, 1H); ESIMS found for $C_{20}H_{23}N_5O$ m/z 350.2 (M+1).

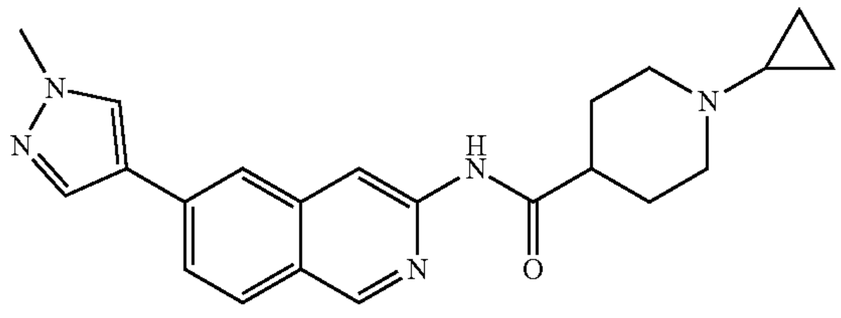
75



1-Isopropyl-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)piperidine-4-carboxamide 75

Off-white solid (43.0 mg, 0.114 mmol, 40.22% yield). ^{1}H NMR (DMSO-d_6, 500 MHz) δ ppm 0.97 (d, J=6.31 Hz, 6H), 1.63 (qd, J=11.98, 3.57 Hz, 2H), 1.78 (br d, J=10.15 Hz, 2H), 2.11 (brt, J=11.11 Hz, 2H), 2.45-2.55 (m, 1H), 2.62-2.73 (m, 1H), 2.83 (br d, J=10.98 Hz, 2H), 3.90 (s, 3H), 7.74 (dd, J=8.51, 1.65 Hz, 1H), 8.00 (d, J=8.51 Hz, 1H), 8.03 (s, 1H), 8.08 (d, J=0.82 Hz, 1H), 8.35 (s, 1H), 8.44 (s, 1H), 9.02 (s, 1H), 10.44 (s, 1H); ESIMS found for $C_{22}H_{27}N_5O$ m/z 378.3 (M+1).

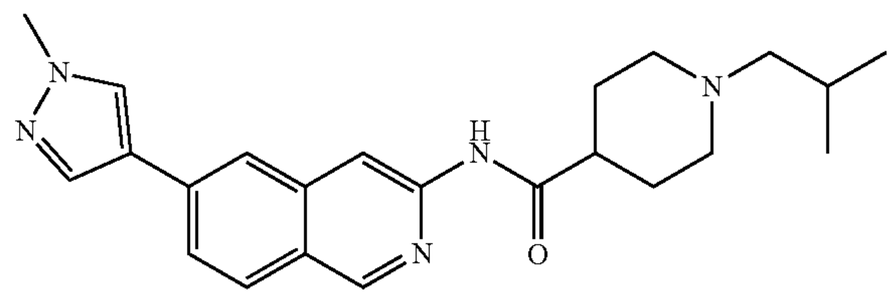
76



1-Cyclopropyl-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)piperidine-4-carboxamide 76

White solid (42.0 mg, 0.112 mmol, 24.6% yield). ^{1}H NMR (DMSO-d_6, 500 MHz) δ ppm 0.25-0.33 (m, 2H), 0.38-0.46 (m, 2H), 1.53-1.65 (m, 3H), 1.76 (br d, J=10.98 Hz, 2H), 2.11-2.22 (m, 2H), 2.51-2.60 (m, 1H), 2.98 (br d, J=11.25 Hz, 2H), 3.90 (s, 3H), 7.74 (dd, J=8.51, 1.65 Hz, 1H), 7.99 (d, J=8.51 Hz, 1H), 8.03 (s, 1H), 8.07 (s, 1H), 8.34 (s, 1H), 8.44 (s, 1H), 9.02 (s, 1H), 10.47 (s, 1H); ESIMS found for $C_{22}H_{25}N_5O$ m/z 376.2 (M+1).

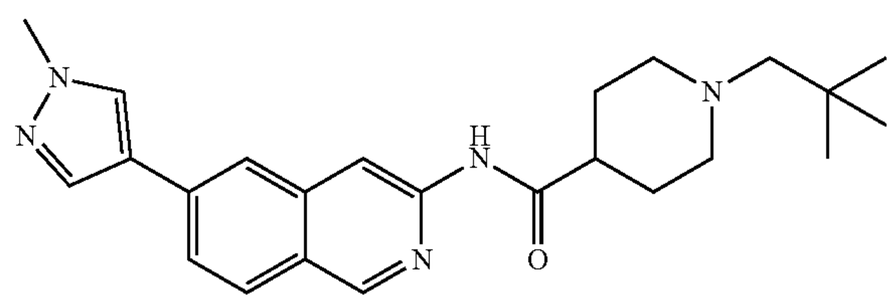
77



1-Isobutyl-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)piperidine-4-carboxamide 77

White solid (128.0 mg, 0.327 mmol, 60.3% yield). ^{1}H NMR (DMSO-d_6, 500 MHz) δ ppm 0.85 (d, J=6.59 Hz, 6H), 1.60-1.73 (m, 2H), 1.73-1.80 (m, 3H), 1.82-1.90 (m, 2H), 2.01 (d, J=7.41 Hz, 2H), 2.51-2.57 (m, 1H), 2.86 (br d, J=11.53 Hz, 2H), 3.90 (s, 3H), 7.74 (dd, J=8.51, 1.37 Hz, 1H), 7.99 (d, J=8.51 Hz, 1H), 8.04 (s, 1H), 8.08 (s, 1H), 8.35 (s, 1H), 8.44 (s, 1H), 9.02 (s, 1H), 10.46 (s, 1H); ESIMS found for $C_{23}H_{29}N_5O$ m/z 392.2 (M+1).

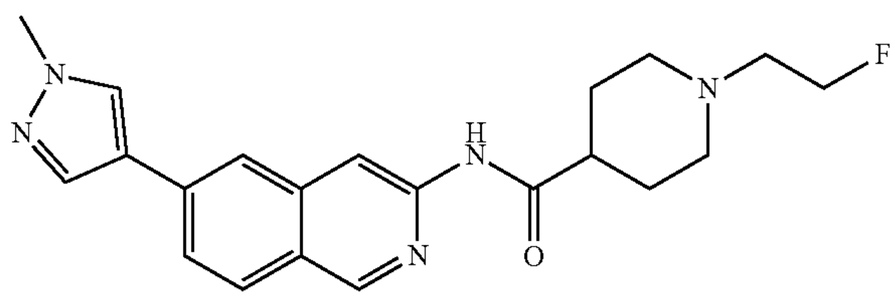
78



N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-1-neopentylpiperidine-4-carboxamide 78

White solid (16.5 mg, 0.041 mmol, 13.7% yield). ^{1}H NMR (DMSO-d_6, 500 MHz) δ ppm 0.85 (s, 9H), 1.67-1.76 (m, 4H), 2.04 (s, 2H), 2.16-2.26 (m, 2H), 2.81 (br d, J=11.25 Hz, 2H), 3.90 (s, 3H), 7.74 (dd, J=8.51, 1.65 Hz, 1H), 7.99 (d, J=8.51 Hz, 1H), 8.04 (s, 1H), 8.08 (s, 1H), 8.35 (s, 1H), 8.44 (s, 1H), 9.02 (s, 1H), 10.45 (s, 1H); ESIMS found for $C_{24}H_{31}N_5O$ m/z 406.3 (M+1).

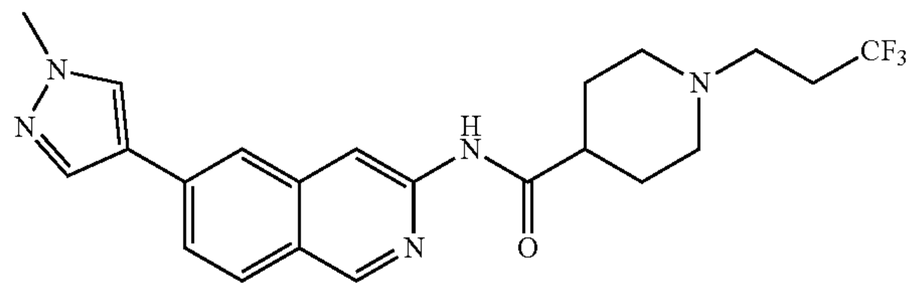
81



1-(2-Fluoroethyl)-N-(6-(1-methyl-1H-pyrazol-4-yl) isoquinolin-3-yl) piperidine-4-carboxamide 81

White solid (257.0 mg, 0.674 mmol, 62.1% yield). ^{1}H NMR (DMSO-d_6, 500 MHz) δ ppm 1.68 (qd, J=12.12, 3.70 Hz, 2H), 1.75-1.83 (m, 2H), 2.03 (td, J=11.66, 2.20 Hz, 2H), 2.51-2.56 (m, 1H), 2.61 (dt, J=28.30, 4.90 Hz, 2H), 2.91-2.99 (m, 2H), 3.90 (s, 3H), 4.53 (dt, J=47.75, 4.95 Hz, 2H), 7.74 (dd, J=8.51, 1.65 Hz, 1H), 8.00 (d, J=8.51 Hz, 1H), 8.03 (s, 1H), 8.07 (s, 1H), 8.34 (s, 1H), 8.44 (s, 1H), 9.02 (s, 1H), 10.46 (s, 1H); ESIMS found for $C_{21}H_{24}FN_5O$ m/z 382.2 (M+1).

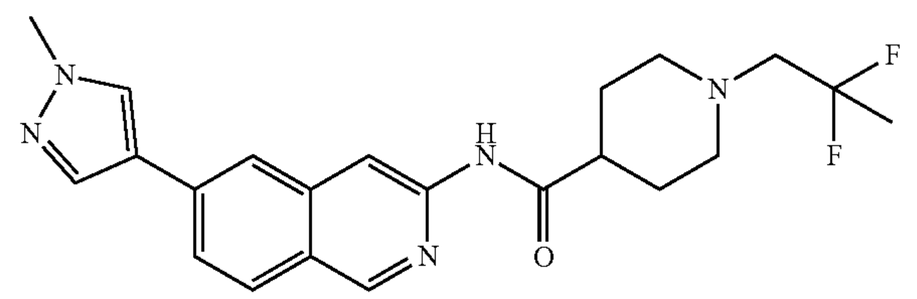
82



N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-1-(3,3,3-trifluoropropyl) piperidine-4-carboxamide 82

White solid (137.0 mg, 0.318 mmol, 54.9% yield). ^{1}H NMR (DMSO-d_6, 500 MHz) δ ppm 1.58-1.74 (m, 2H), 1.79 (br d, J=10.70 Hz, 2H), 1.92-2.02 (m, 2H), 2.40-2.60 (m, 5H), 2.93 (br d, J=11.25 Hz, 2H), 3.90 (s, 3H), 7.74 (dd, J=8.51, 1.37 Hz, 1H), 8.00 (d, J=8.51 Hz, 1H), 8.03 (s, 1H), 8.08 (s, 1H), 8.35 (s, 1H), 8.44 (s, 1H), 9.02 (s, 1H), 10.48 (s, 1H); ESIMS found for $C_{22}H_{24}F_3N_5O$ m/z 432.2 (M+1).

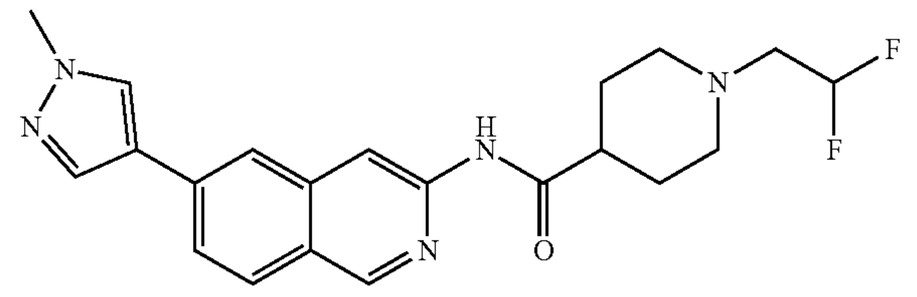
83



1-(2,2-Difluoropropyl)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl) piperidine-4-carboxamide 83

Off-white solid (29.0 mg, 0.070 mmol, 23.5% yield). ^{1}H NMR (DMSO-d_6, 500 MHz) δ ppm 1.62 (t, J=19.21 Hz, 3H), 1.66-1.73 (m, 2H), 1.73-1.81 (m, 2H), 2.21 (td, J=11.66, 2.47 Hz, 2H), 2.50-2.57 (m, 1H), 2.70 (t, J=14.00 Hz, 2H), 2.94 (br d, J=11.53 Hz, 2H), 3.89 (s, 3H), 7.74 (dd, J=8.51, 1.65 Hz, 1H), 7.99 (d, J=8.51 Hz, 1H), 8.03 (s, 1H), 8.07 (d, J=0.82 Hz, 1H), 8.34 (s, 1H), 8.43 (s, 1H), 9.01 (s, 1H), 10.48 (s, 1H); ESIMS found for $C_{22}H_{25}F_2N_5O$ m/z 414.2 (M+1).

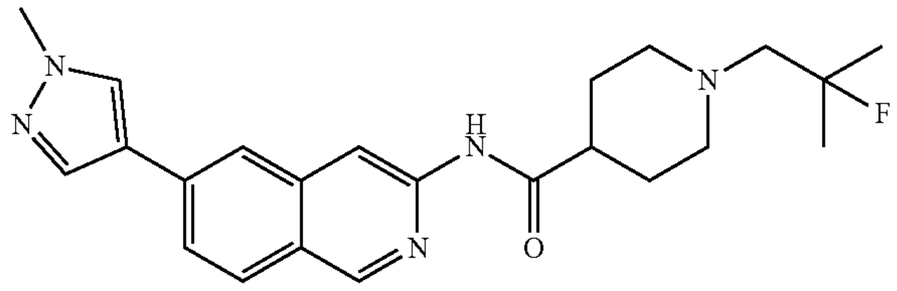
84



1-(2,2-Difluoroethyl)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl) piperidine-4-carboxamide 84

White solid (147.0 mg, 0.368 mmol, 7.71% yield). ^{1}H NMR (DMSO-d_6, 500 MHz) δ ppm 1.68 (qd, J=12.12, 3.70 Hz, 2H), 1.74-1.83 (m, 2H), 2.14-2.23 (m, 2H), 2.52-2.59 (m, 1H), 2.72 (td, J=15.57, 4.25 Hz, 2H), 2.96 (br d, J=11.53 Hz, 2H), 3.90 (s, 3H), 6.13 (tt, J=55.75, 4.15 Hz, 1H), 7.74 (dd, J=8.51, 1.65 Hz, 1H), 8.00 (d, J=8.51 Hz, 1H), 8.03 (s, 1H), 8.07 (s, 1H), 8.34 (s, 1H), 8.44 (s, 1H), 9.02 (s, 1H), 10.47 (s, 1H); ESIMS found for $C_{21}H_{23}F_2N_5O$ m/z 400.2 (M+1).

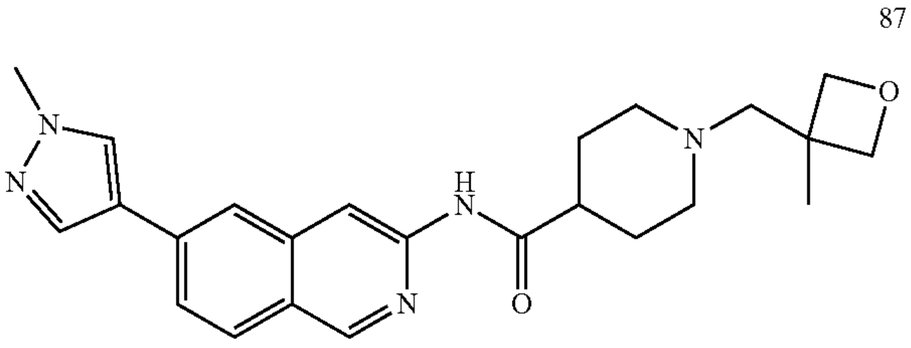
85



1-(2-Fluoro-2-methylpropyl)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)piperidine-4-carboxamide 85

Off-white solid (110.0 mg, 0.269 mmol, 47.4% yield). ^{1}H NMR (DMSO-d_6, 500 MHz) δ ppm 1.31 (d, J=21.45 Hz, 6H), 1.64-1.81 (m, 4H), 2.10 (td, J=11.53, 2.74 Hz, 2H), 2.45 (t, J=22.85 Hz, 2H), 2.51-2.57 (m, 1H), 2.95 (br d, J=11.53 Hz, 2H), 3.90 (s, 3H), 7.74 (dd, J=8.51, 1.37 Hz, 1H), 8.00 (d, J=8.51 Hz, 1H), 8.04 (s, 1H), 8.08 (s, 1H), 8.35 (s, 1H), 8.44 (s, 1H), 9.02 (s, 1H), 10.46 (s, 1H); ESIMS found for $C_{23}H_{28}FN_5O$ m/z 410.2 (M+1).

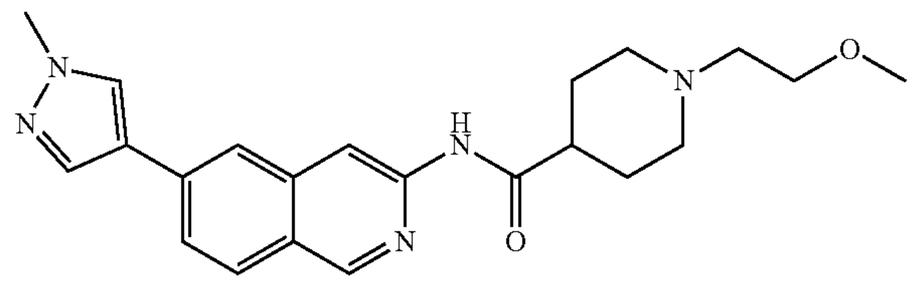
87



N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-1-((3-methyloxetan-3-yl) methyl)piperidine-4-carboxamide 87

White solid (58.0 mg, 0.138 mmol, 57.8% yield). ^{1}H NMR (DMSO-d_6, 500 MHz) δ ppm 1.31 (s, 3H), 1.59-1.70 (m, 2H), 1.71-1.79 (m, 2H), 1.97 (td, J=11.53, 2.47 Hz, 2H), 2.48 (s, 2H), 2.51-2.57 (m, 1H), 2.62 (br d, J=11.25 Hz, 2H), 3.90 (s, 3H), 4.19 (d, J=5.49 Hz, 2H), 4.36 (d, J=5.76 Hz, 2H), 7.74 (dd, J=8.51, 1.65 Hz, 1H), 8.00 (d, J=8.51 Hz, 1H), 8.04 (s, 1H), 8.08 (s, 1H), 8.35 (s, 1H), 8.44 (s, 1H), 9.02 (s, 1H), 10.47 (s, 1H); ESIMS found for $C_{24}H_{29}N_5O_2$ m/z 420.3 (M+1).

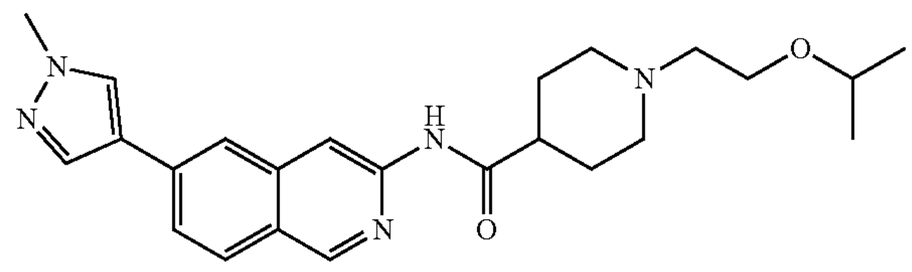
89



1-(2-Methoxyethyl)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl) piperidine-4-carboxamide 89

White solid (32.0 mg, 0.081 mmol, 28.7% yield). ^{1}H NMR (DMSO-d_6, 500 MHz) δ ppm 1.59-1.71 (m, 2H), 1.73-1.81 (m, 2H), 1.92-2.04 (m, 2H), 2.46 (t, J=5.90 Hz, 2H), 2.51-2.58 (m, 1H), 2.92 (br d, J=11.25 Hz, 2H), 3.24 (s, 3H), 3.43 (t, J=6.04 Hz, 2H), 3.90 (s, 3H), 7.74 (dd, J=8.51, 1.65 Hz, 1H), 8.00 (d, J=8.51 Hz, 1H), 8.03 (s, 1H), 8.08 (d, J=0.82 Hz, 1H), 8.35 (s, 1H), 8.44 (s, 1H), 9.02 (s, 1H), 10.46 (s, 1H); ESIMS found for $C_{22}H_{27}N_5O_2$ m/z 394.2 (M+1).

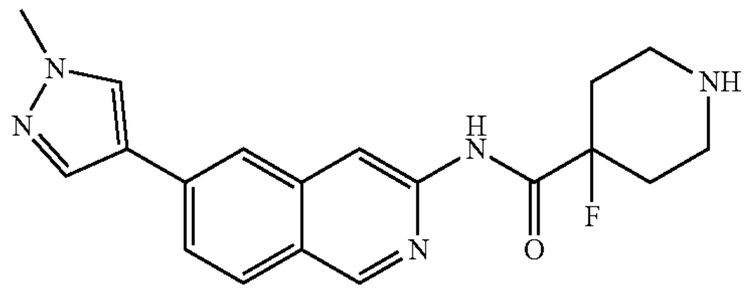
90



1-(2-Isopropoxyethyl)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl) piperidine-4-carboxamide 90

Off-white solid (71.0 mg, 0.168 mmol, 56.5% yield). ^{1}H NMR (DMSO-d_6, 500 MHz) δ ppm 1.08 (d, J=6.04 Hz, 7H), 1.59-1.71 (m, 2H), 1.73-1.82 (m, 2H), 1.98 (td, J=11.60, 2.06 Hz, 2H), 2.44 (t, J=6.17 Hz, 2H), 2.51-2.58 (m, 1H), 2.92 (br d, J=11.53 Hz, 2H), 3.46 (t, J=6.31 Hz, 2H), 3.53 (dt, J=12.14, 6.14 Hz, 1H), 3.90 (s, 3H), 7.74 (dd, J=8.64, 1.51 Hz, 1H), 7.99 (d, J=8.51 Hz, 1H), 8.03 (s, 1H), 8.08 (s, 1H), 8.35 (s, 1H), 8.44 (s, 1H), 9.02 (s, 1H), 10.45 (s, 1H); ESIMS found for $C_{24}H_{31}N_5O_2$ m/z 422.2 (M+1).

91

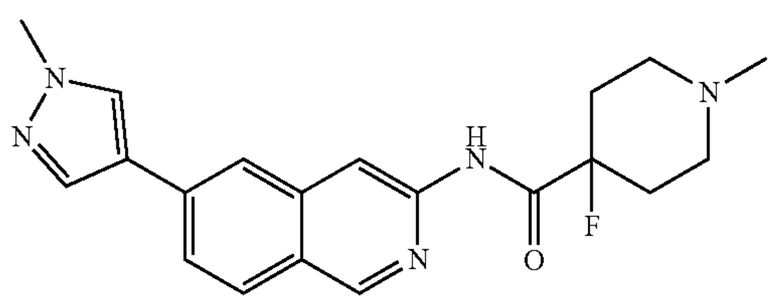


4-Fluoro-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)piperidine-4-carboxamide 91

White solid (54.0 mg, 0.153 mmol). ^{1}H NMR (DMSO-d_6, 500 MHz) δ ppm 1.79-1.90 (m, 2H), 1.93-2.12 (m, 2H), 2.74 (td, J=12.28, 2.33 Hz, 2H), 2.86-2.94 (m, 2H), 3.90 (s, 3H), 7.81 (dd, J=8.64, 1.51 Hz, 1H), 8.05 (d, J=8.51 Hz, 1H), 8.09

(s, 1H), 8.12 (s, 1H), 8.36 (s, 1H), 8.40 (s, 1H), 9.08 (s, 1H), 9.78 (d, J=4.39 Hz, 1H); ESIMS found for $C_{19}H_{20}FN_5O$ m/z 354.2 (M+1).

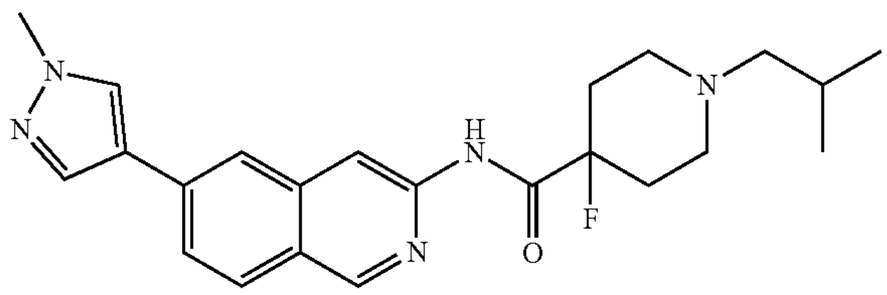
92



4-Fluoro-1-methyl-N-(6-(1-methyl-1H-pyrazol-4-yl) isoquinolin-3-yl) piperidine-4-carboxamide 92

White solid (57.0 mg, 0.155 mmol, 68.5% yield). ^{1}H NMR (DMSO-d_6, 500 MHz) δ ppm 1.89-2.01 (m, 2H), 2.05-2.20 (m, 4H), 2.22 (s, 3H), 2.69-2.77 (m, 2H), 3.91 (s, 3H), 7.81 (dd, J=8.51, 1.37 Hz, 1H), 8.05 (d, J=8.78 Hz, 1H), 8.09 (s, 1H), 8.11 (s, 1H), 8.36 (s, 1H), 8.40 (s, 1H), 9.08 (s, 1H), 9.87 (d, J=4.12 Hz, 1H); ESIMS found for $C_{20}H_{22}FN_5O$ m/z 368.2 (M+1).

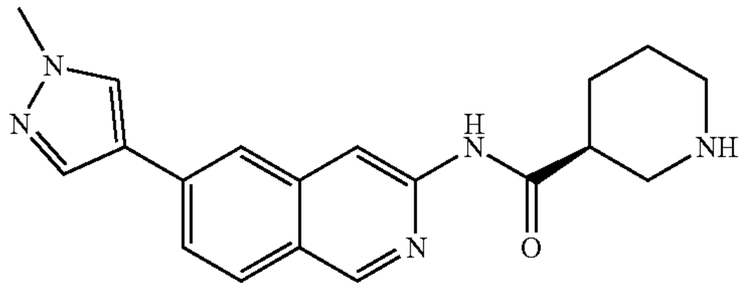
96



4-Fluoro-1-isobutyl-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl) piperidine-4-carboxamide 96

White solid (37.0 mg, 0.090 mmol, 39.9% yield). ^{1}H NMR (DMSO-d_6, 500 MHz) δ ppm 0.88 (d, J=6.59 Hz, 6H), 1.74-1.85 (m, 1H), 1.91-2.01 (m, 2H), 2.09 (d, J=7.41 Hz, 2H), 2.11-2.21 (m, 4H), 2.78 (br d, J=8.23 Hz, 2H), 3.90 (s, 3H), 7.81 (dd, J=8.51, 1.65 Hz, 1H), 8.05 (d, J=8.51 Hz, 1H), 8.10 (s, 1H), 8.12 (s, 1H), 8.37 (s, 1H), 8.40 (s, 1H), 9.08 (s, 1H), 9.86 (d, J=4.39 Hz, 1H); ESIMS found for $C_{23}H_{28}FN_5O$ m/z 410.2 (M+1).

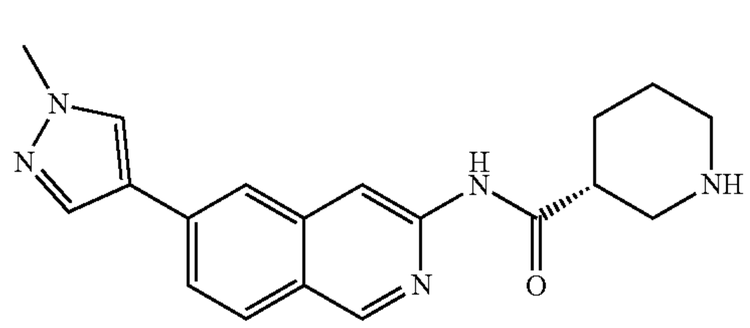
110



(S)—N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)piperidine-3-carboxamide 110

White solid (37.7 mg, 0.112 mmol, 47.0% yield). ^{1}H NMR (DMSO-d_6, 500 MHz) δ ppm 1.34-1.48 (m, 1H), 1.55-1.64 (m, 1H), 1.64-1.73 (m, 1H), 1.81-1.92 (m, 1H), 2.52-2.67 (m, 2H), 2.71-2.85 (m, 2H), 2.98 (dd, J=11.94, 3.16 Hz, 1H), 3.90 (s, 3H), 7.74 (dd, J=8.51, 1.65 Hz, 1H), 8.00 (d, J=8.51 Hz, 1H), 8.03 (s, 1H), 8.08 (s, 1H), 8.35 (s, 1H), 8.42 (s, 1H), 9.01 (s, 1H), 10.75 (s, 1H); ESIMS found for $C_{19}H_{21}N_5O$ m/z 336.1 (M+1).

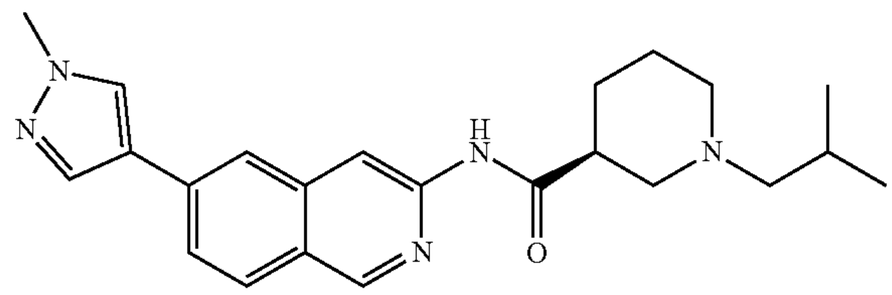
111



(R)—N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)piperidine-3-carboxamide 111

White solid (6.5 mg, 0.019 mmol, 44.8% yield). ^{1}H NMR (DMSO-d_6, 500 MHz) δ ppm 1.33-1.49 (m, 1H), 1.55-1.64 (m, 1H), 1.64-1.74 (m, 1H), 1.81-1.93 (m, 1H), 2.52-2.66 (m, 2H), 2.71-2.86 (m, 2H), 2.98 (dd, J=11.80, 2.74 Hz, 1H), 3.90 (s, 3H), 7.74 (dd, J=8.64, 1.51 Hz, 1H), 8.00 (d, J=8.51 Hz, 1H), 8.03 (s, 1H), 8.08 (s, 1H), 8.35 (s, 1H), 8.42 (s, 1H), 9.01 (s, 1H), 10.75 (s, 1H); ESIMS found for $C_{19}H_{21}N_5O$ m/z 336.2 (M+1).

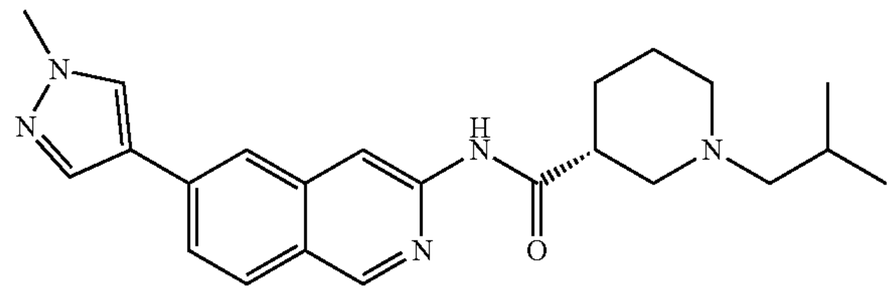
112



(S)-1-Isobutyl-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)piperidine-3-carboxamide 112

Beige solid (17.8 mg, 0.045 mmol, 4.7% yield). ^{1}H NMR (DMSO-d_6, 500 MHz) δ ppm 0.88 (d, J=6.59 Hz, 3H), 0.90 (d, J=6.59 Hz, 3H), 1.48-1.60 (m, 2H), 1.64-1.73 (m, 1H), 1.77-1.86 (m, 2H), 2.07 (d, J=7.41 Hz, 2H), 2.10 (br dd, J=4.25, 3.16 Hz, 1H), 2.30 (br d, J=7.14 Hz, 1H), 2.55-2.63 (m, 1H), 2.76 (br d, J=7.68 Hz, 2H), 3.90 (s, 3H), 7.74 (dd, J=8.51, 1.65 Hz, 1H), 8.00 (d, J=8.78 Hz, 1H), 8.04 (s, 1H), 8.08 (s, 1H), 8.35 (s, 1H), 8.42 (s, 1H), 9.01 (s, 1H), 10.68 (s, 1H); ESIMS found for $C_{23}H_{29}N_5O$ m/z 392.2 (M+1).

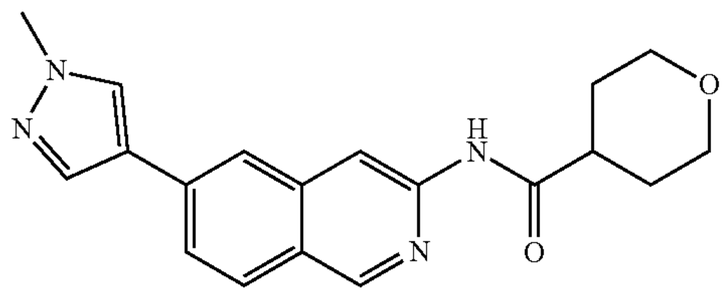
113



(R)-1-Isobutyl-N-(6-(1-methyl-1H-pyrazol-4-yl) isoquinolin-3-yl)piperidine-3-carboxamide 113

Beige solid (110 mg, 0.281 mmol, 26.8% yield). ^{1}H NMR (DMSO-d_6, 500 MHz) δ ppm 0.88 (3H, d, J=6.59 Hz), 0.90 (3H, d, J=6.59 Hz), 1.49-1.59 (2H, m), 1.68 (1H, br dd, J=8.23, 3.29 Hz), 1.76-1.88 (2H, m), 2.07 (2H, d, J=7.41 Hz), 2.10 (1H, br s), 2.30 (1H, br d, J=6.59 Hz), 2.55-2.62 (1H, m), 2.76 (2H, br d, J=7.68 Hz), 3.90 (3H, s), 7.74 (1H, dd, J=8.51, 1.37 Hz), 8.00 (1H, d, J=8.51 Hz), 8.04 (1H, s), 8.08 (1H, s), 8.35 (1H, s), 8.42 (1H, s), 9.01 (1H, s), 10.68 (1H, s); ESIMS found for $C_{23}H_{29}N_5O$ m/z 392.2 (M+1).

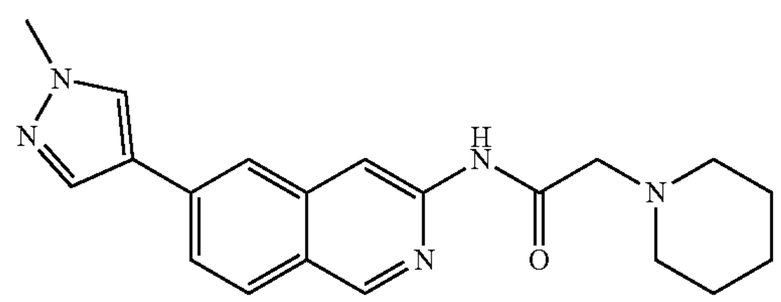
114



N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl) tetrahydro-2H-pyran-4-carboxamide 114

White solid (95.0 mg, 0.282 mmol, 63.3% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.62-1.80 (m, 4H), 2.76-2.87 (m, 1H), 3.32-3.38 (m, 2H), 3.90 (s, 3H), 3.91-3.95 (m, 2H), 7.74 (dd, J=8.51, 1.65 Hz, 1H), 8.00 (d, J=8.51 Hz, 1H), 8.04 (s, 1H), 8.08 (s, 1H), 8.35 (s, 1H), 8.44 (s, 1H), 9.03 (s, 1H), 10.49 (s, 1H); ESIMS found for $C_{19}H_{20}N_4O_2$ m/z 337.15 (M+1).

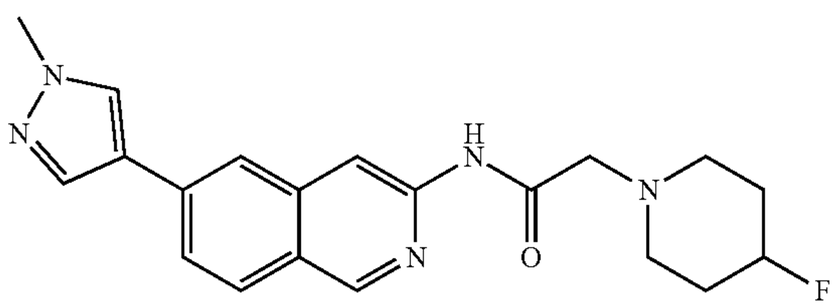
115



N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(piperidin-1-yl) acetamide 115

Off-white solid (23.0 mg, 0.066 mmol, 16.5% yield). ^{1}H NMR (DMSO-d_6, 500 MHz) δ ppm 1.43 (2H, br d, J=4.39 Hz), 1.59 (4H, quin, J=5.56 Hz), 2.52 (4H, br s), 3.17 (2H, s), 3.90 (3H, s), 7.77 (1H, dd, J=8.51, 1.37 Hz), 8.02 (1H, d, J=8.51 Hz), 8.10 (2H, s), 8.37 (1H, s), 8.43 (1H, s), 9.04 (1H, s), 9.91 (1H, s); ESIMS found for $C_{20}H_{23}N_5O$ m/z 350.2 (M+1).

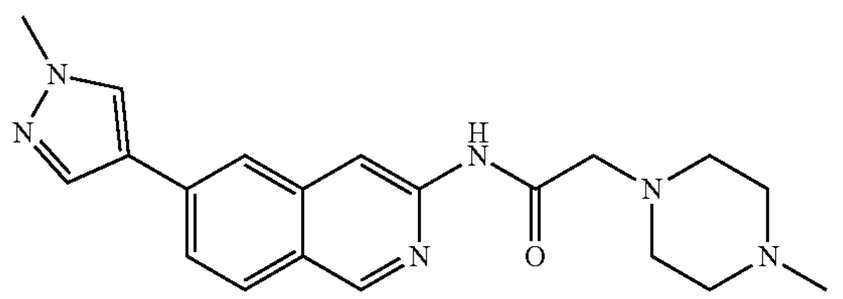
116



2-(4-Fluoropiperidin-1-yl)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)acetamide 116

Off-white solid (80.0 mg, 0.218 mmol, 44.3% yield). ^{1}H NMR (DMSO-d_6, 500 MHz) δ ppm 1.73-1.86 (2H, m), 1.87-2.01 (2H, m), 2.54 (2H, ddd, J=11.39, 7.41, 3.70 Hz), 2.67-2.76 (2H, m), 3.24 (2H, s), 4.66-4.83 (1H, m), 7.77 (1H, dd, J=8.51, 1.65 Hz), 8.02 (1H, d, J=8.51 Hz), 8.10 (2H, s), 8.36 (1H, s), 8.44 (1H, s), 9.04 (1H, s), 9.98 (1H, s); ESIMS found for $C_{20}H_{22}FN_5O$ m/z 368.2 (M+1).

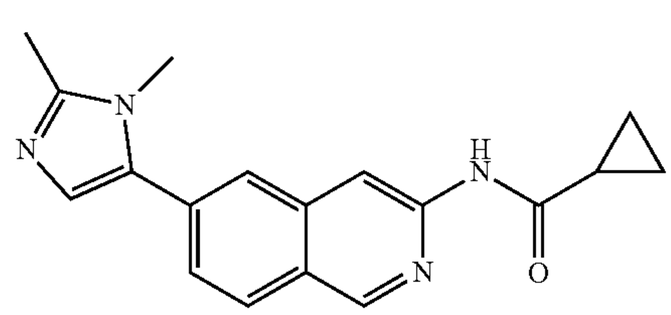
118



N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(4-methylpiperazin-1-yl)acetamide 118

Beige solid (18.0 mg, 0.049 mmol, 59.8% yield). ^{1}H NMR (DMSO-d_6, 500 MHz) δ ppm 2.19 (3H, s), 2.33-2.46 (4H, m), 2.58 (4H, br s), 3.22 (2H, s), 3.90 (3H, s), 7.77 (1H, dd, J=8.51, 1.65 Hz), 8.02 (1H, d, J=8.51 Hz), 8.10 (2H, s), 8.37 (1H, s), 8.43 (1H, s), 9.04 (1H, s), 9.93 (1H, s); ESIMS found for $C_{20}H_{24}N_6O$ m/z 365.2 (M+1).

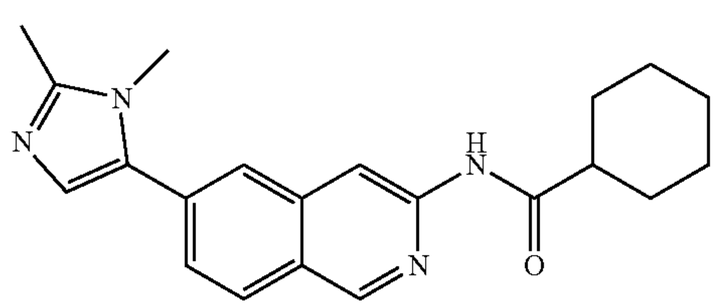
119



N-(6-(1,2-Dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl) cyclopropanecarboxamide 119

Beige solid (70.0 mg, 0.228 mmol, 28.9% yield). ^{1}H NMR (DMSO-d_6, 500 MHz) δ ppm 0.78-0.91 (4H, m), 2.02-2.13 (1H, m), 2.39 (3H, s), 3.65 (3H, s), 7.11 (1H, s), 7.59 (1H, dd, J=8.51, 1.37 Hz), 7.88 (1H, s), 8.07 (1H, d, J=8.51 Hz), 8.49 (1H, s), 9.12 (1H, s), 10.89 (1H, s); ESIMS found for $C_{18}H_{18}N_4O$ m/z 307.1 (M+1).

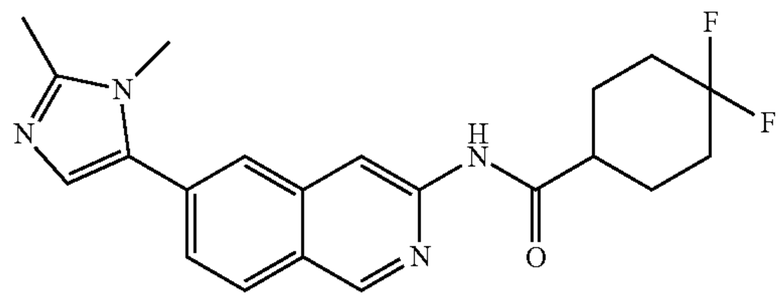
120



N-(6-(1,2-Dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl) cyclohexanecarboxamide 120

Beige solid (20.0 mg, 0.056 mmol, 18.7% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.17-1.34 (3H, m), 1.44 (2H, qd, J=12.21, 2.61 Hz), 1.66 (1H, br d, J=11.53 Hz), 1.71-1.79 (2H, m), 1.83 (2H, br d, J=13.17 Hz), 2.39 (3H, br s), 2.52-2.62 (1H, m), 3.66 (3H, s), 7.13 (1H, br s), 7.58 (1H, dd, J=8.51, 1.37 Hz), 7.89 (1H, s), 8.07 (1H, d, J=8.51 Hz), 8.51 (1H, s), 9.11 (1H, s), 10.43 (1H, s); ESIMS found for $C_{21}H_{24}N_4O$ m/z 349.0 (M+1).

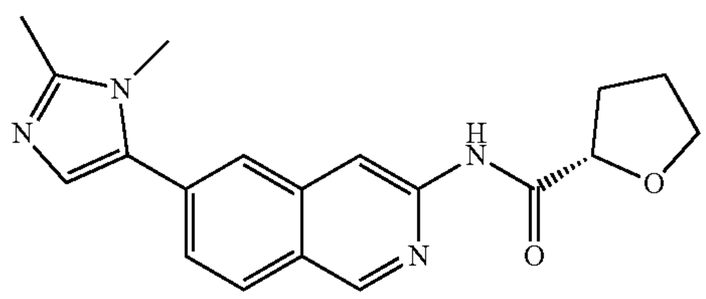
121



N-(6-(1,2-Dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-4,4-difluorocyclohexanecarboxamide 121

Off-white solid (40.0 mg, 0.104 mmol, 38.4% yield). ^{1}H NMR (DMSO-d_6, 500 MHz) δ ppm 1.66-1.76 (2H, m), 1.77-1.91 (2H, m), 1.92-2.01 (2H, m), 2.08-2.21 (2H, m), 2.39 (3H, s), 2.71 (1H, br t, J=10.43 Hz), 3.66 (3H, s), 7.12 (1H, br s), 7.61 (1H, dd, J=8.51, 1.37 Hz), 7.91 (1H, s), 8.08 (1H, d, J=8.51 Hz), 8.51 (1H, s), 9.12 (1H, s), 10.63 (1H, s); ESIMS found for $C_{21}H_{22}F_2N_4O$ m/z 385.2 (M+1).

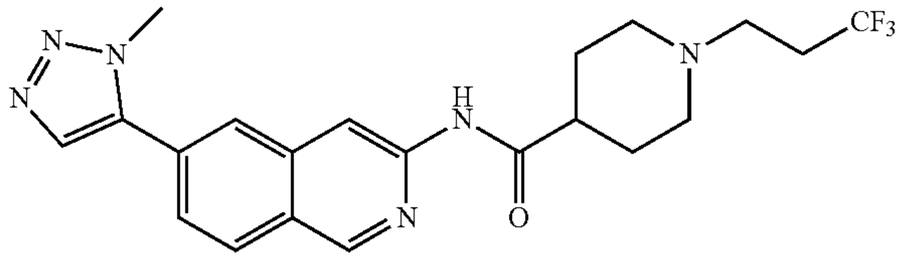
188



(S)—N-(6-(1,2-Dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)tetrahydrofuran-2-carboxamide 188

Light yellow solid (60.0 mg, 0.178 mmol, 57.3% yield). ^{1}H NMR (DMSO-d_6, 500 MHz) δ ppm 1.83-1.95 (2H, m), 1.97-2.07 (1H, m), 2.19-2.30 (1H, m), 2.39 (3H, s), 3.67 (3H, s), 3.82-3.91 (1H, m), 3.98-4.07 (1H, m), 4.54 (1H, dd, J=8.23, 5.49 Hz), 7.13 (1H, s), 7.64 (1H, dd, J=8.51, 1.65 Hz), 7.96 (1H, s), 8.11 (1H, d, J=8.51 Hz), 8.50 (1H, s), 9.14 (1H, s), 9.85 (1H, s); ESIMS found for $C_{19}H_{20}N_4O_2$ m/z 337.1 (M+1).

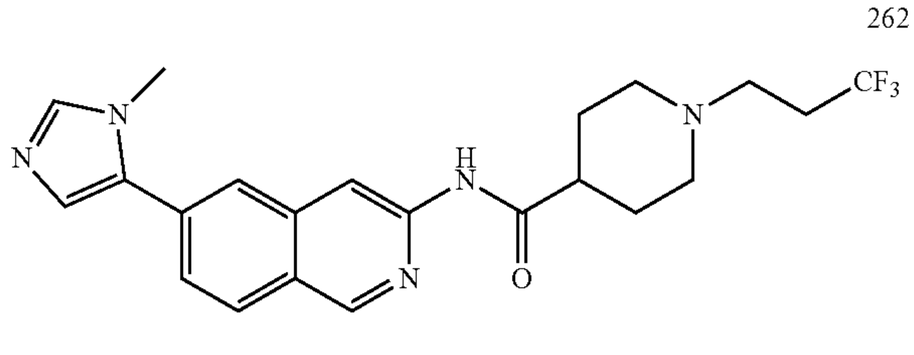
248



N-(6-(1-Methyl-1H-1,2,3-triazol-5-yl)isoquinolin-3-yl)-1-(3,3,3-trifluoropropyl)piperidine-4-carboxamide 248

Off-white solid (99.0 mg, 0.229 mmol, 50.3% yield). ^{1}H NMR (DMSO-d_6, 500 MHz) δ ppm 1.61-1.74 (m, 2H), 1.80 (br d, J=10.70 Hz, 2H), 1.97 (br t, J=11.11 Hz, 2H), 2.40-2.61 (m, 5H), 2.89-3.00 (m, 2H), 4.20 (s, 3H), 7.68-7.77 (m, 1H), 8.10 (s, 1H), 8.17-8.21 (m, 2H), 8.60 (s, 1H), 9.21 (s, 1H), 10.62 (br s, 1H); ESIMS found for $C_{21}H_{23}F_3N_6O$ m/z 433.2 (M+1).

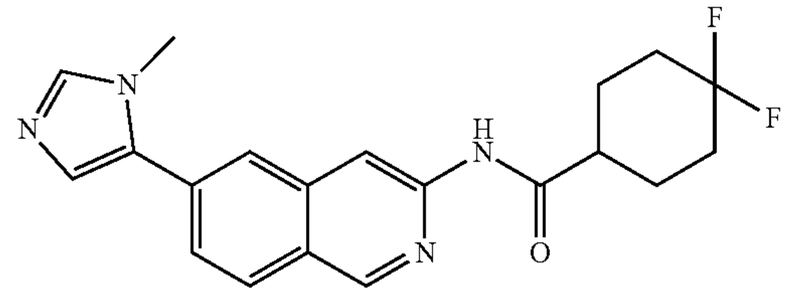
262



N-(6-(1-Methyl-1H-imidazol-5-yl)isoquinolin-3-yl)-1-(3,3,3-trifluoropropyl) piperidine-4-carboxamide 262

White solid (82.5 mg, 0.191 mmol, 82.4% yield). ^{1}H NMR (DMSO-d_6, 500 MHz) δ ppm 1.68 (qd, J=12.17, 3.57 Hz, 2H), 1.81 (br d, J=11.25 Hz, 2H), 1.97-2.11 (m, 2H), 2.50 (dt, J=3.64, 1.89 Hz, 2H), 2.52-2.62 (m, 3H), 2.97 (br d, J=10.43 Hz, 2H), 3.83 (s, 3H), 7.30 (d, J=0.82 Hz, 1H), 7.67 (dd, J=8.51, 1.65 Hz, 1H), 7.80 (s, 1H), 8.00 (s, 1H), 8.08 (d, J=8.51 Hz, 1H), 8.54 (s, 1H), 9.12 (s, 1H), 10.55 (s, 1H); ESIMS found for $C_{22}H_{24}F_3N_5O$ m/z 432.2 (M+1).

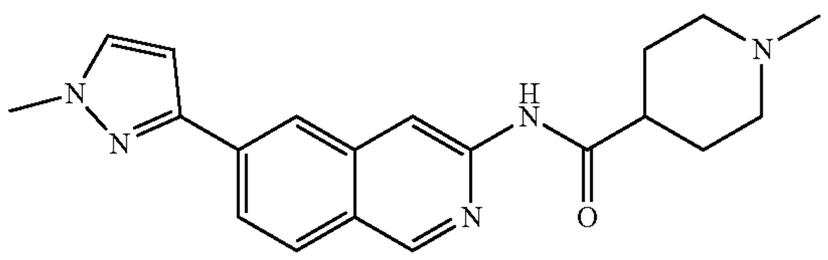
263



4,4-Difluoro-N-(6-(1-methyl-1H-imidazol-5-yl)isoquinolin-3-yl) cyclohexanecarboxamide 263

White solid (60.0 mg, 0.162 mmol, 46.0% yield). ^{1}H NMR (DMSO-d_6, 500 MHz) δ ppm 1.63-1.76 (m, 2H), 1.76-1.91 (m, 2H), 1.95 (br d, J=12.90 Hz, 2H), 2.06-2.20 (m, 2H), 2.71 (br t, J=10.84 Hz, 1H), 3.83 (s, 3H), 7.30 (d, J=0.82 Hz, 1H), 7.67 (dd, J=8.37, 1.78 Hz, 1H), 7.79 (s, 1H), 8.01 (d, J=0.82 Hz, 1H), 8.09 (d, J=8.78 Hz, 1H), 8.53 (s, 1H), 9.13 (s, 1H), 10.64 (s, 1H); ESIMS found for $C_{20}H_{20}F_2N_4O$ m/z 371.2 (M+1).

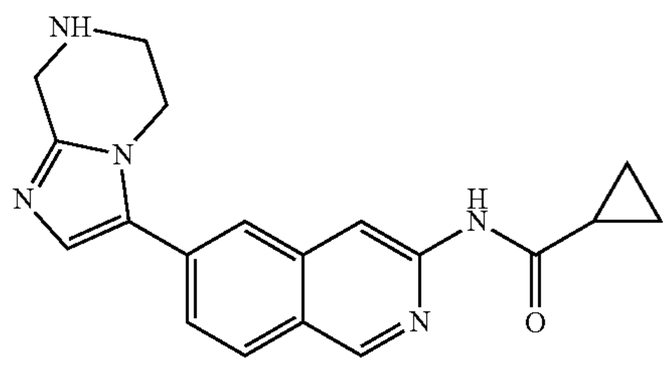
264



1-Methyl-N-(6-(1-methyl-1H-pyrazol-3-yl)isoquinolin-3-yl)piperidine-4-carboxamide 264

White solid (36.5 mg, 0.104 mmol, 48.5% yield). ^{1}H NMR (DMSO-d_6, 500 MHz) δ ppm 1.60-1.72 (m, 2H), 1.74-1.80 (m, 2H), 1.86 (td, J=11.60, 2.06 Hz, 2H), 2.16 (s, 3H), 2.45-2.56 (m, 1H), 2.81 (br d, J=11.25 Hz, 2H), 3.93 (s, 3H), 6.93 (d, J=2.20 Hz, 1H), 7.81 (d, J=2.20 Hz, 1H), 7.95-8.01 (m, 1H), 8.01-8.08 (m, 1H), 8.20 (s, 1H), 8.49 (s, 1H), 9.07 (s, 1H), 10.49 (s, 1H); ESIMS found for $C_{20}H_{23}N_5O$ m/z 350.2 (M+1).

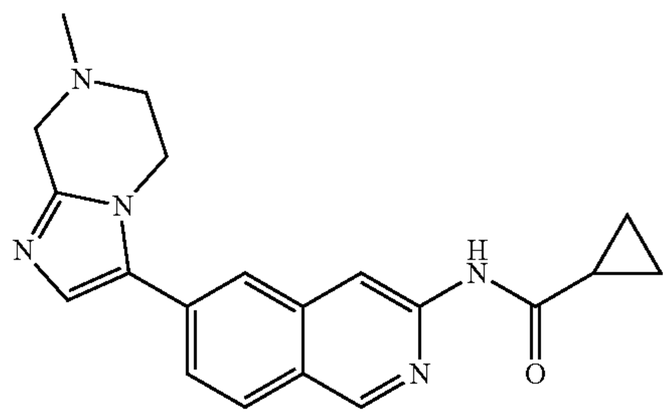
265



N-(6-(5,6,7,8-Tetrahydroimidazo[1,2-a]pyrazin-3-yl) isoquinolin-3-yl) cyclopropanecarboxamide 265

Off-white solid (168.0 mg, 0.504 mmol, 87.3% yield). ^{1}H NMR (DMSO-d_6, 500 MHz) δ ppm 0.78-0.90 (m, 4H), 2.03-2.13 (m, 1H), 2.77 (br s, 1H), 3.07 (t, J=5.35 Hz, 2H), 3.95 (s, 2H), 4.10 (t, J=5.35 Hz, 2H), 7.28 (s, 1H), 7.65 (dd, J=8.51, 1.65 Hz, 1H), 7.91 (s, 1H), 8.06 (d, J=8.51 Hz, 1H), 8.49 (s, 1H), 9.10 (s, 1H), 10.87 (s, 1H); ESIMS found for $C_{19}H_{19}N_5O$ m/z 334.1 (M+1).

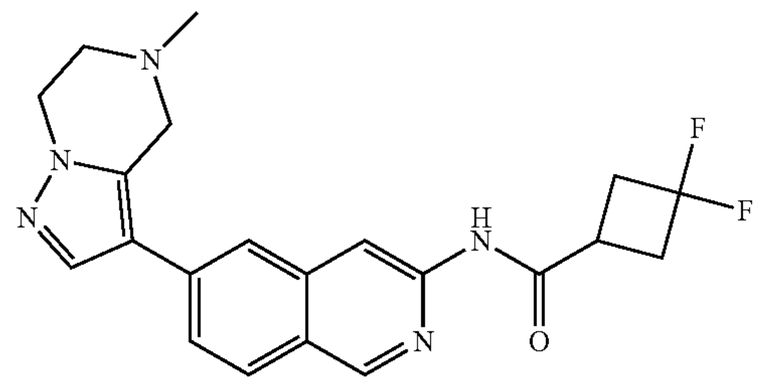
266



N-(6-(7-Methyl-5,6,7,8-tetrahydroimidazo[1,2-a] pyrazin-3-yl)isoquinolin-3-yl)cyclopropanecarboxamide 266

White solid (75.0 mg, 0.216 mmol, 69.9% yield). ^{1}H NMR (DMSO-d_6, 500 MHz) δ ppm 0.77-0.90 (m, 4H), 2.01-2.13 (m, 1H), 2.42 (s, 3H), 2.80 (t, J=5.35 Hz, 2H), 3.63 (s, 2H), 4.21 (t, J=5.35 Hz, 2H), 7.29 (s, 1H), 7.66 (dd, J=8.51, 1.65 Hz, 1H), 7.95 (s, 1H), 8.06 (d, J=8.51 Hz, 1H), 8.49 (s, 1H), 9.10 (s, 1H), 10.87 (s, 1H); ESIMS found for $C_{20}H_{21}N_5O$ m/z 348.2 (M+1).

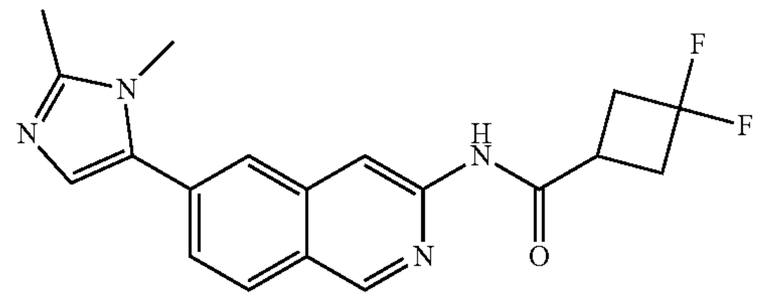
267



3,3-Difluoro-N-(6-(5-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-3-yl) isoquinolin-3-yl)cyclobutanecarboxamide 267

Beige solid (65.0 mg, 0.164 mmol, 28.5% yield). ^{1}H NMR (DMSO-d_6, 500 MHz) δ ppm 2.55 (br s, 2H), 2.75-2.88 (m, 4H), 2.93-3.10 (m, 1H), 3.94-4.10 (m, 1H), 4.21 (br s, 2H), 7.66 (dd, J=8.51, 1.65 Hz, 1H), 7.79 (s, 1H), 8.02 (s, 1H), 8.05 (d, J=8.51 Hz, 1H), 8.52 (s, 1H), 9.08 (s, 1H), 10.76 (s, 1H); ESIMS found for $C_{21}H_{21}F_2N_5O$ m/z 398.2 (M+1).

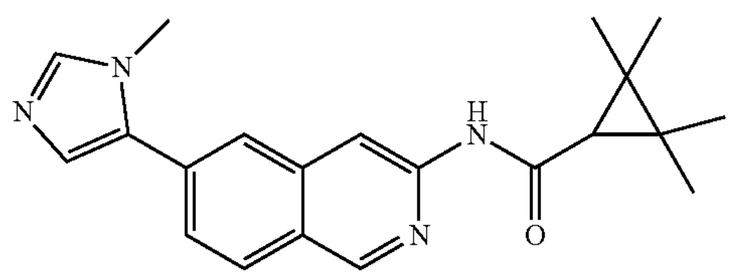
268



N-(6-(1,2-Dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-3,3-difluorocyclobutanecarboxamide 268

White solid (67.0 mg, 0.188 mmol, 49.3% yield). ^{1}H NMR (DMSO-d_6, 500 MHz) δ ppm 2.39 (s, 3H), 2.76-2.92 (m, 4H), 3.27-3.36 (m, 1H), 3.67 (s, 3H), 7.12 (s, 1H), 7.62 (dd, J=8.51, 1.65 Hz, 1H), 7.93 (s, 1H), 8.09 (d, J=8.51 Hz, 1H), 8.55 (s, 1H), 9.13 (s, 1H), 10.80 (s, 1H); ESIMS found for $C_{19}H_{18}F_2N_4O$ m/z 357.1 (M+1).

269

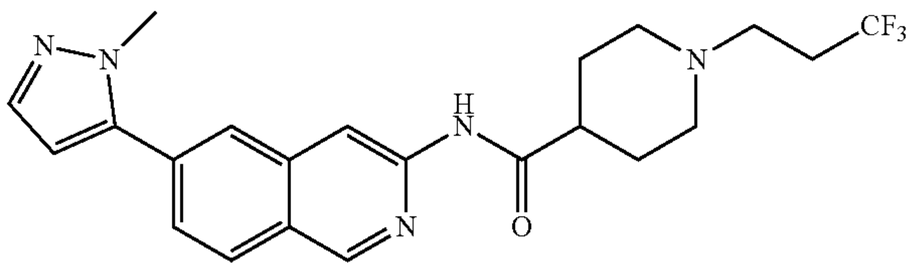


2,2,3,3-Tetramethyl-N-[6-(3-methylimidazol-4-yl)-3-isoquinolyl]cyclopropanecarboxamide 269

Light yellow solid (132.0 mg, 0.379 mmol, 65.3% yield). ^{1}H NMR (DMSO-d_6, 500 MHz) δ ppm 1.19 (s, 6H), 1.28 (s,

6H), 1.63 (s, 1H), 3.83 (s, 3H), 7.26-7.40 (m, 1H), 7.64 (dd, J=8.51, 1.37 Hz, 1H), 7.75-7.87 (m, 1H), 8.00 (s, 1H), 8.06 (d, J=8.51 Hz, 1H), 8.52 (s, 1H), 9.09 (s, 1H), 10.51 (s, 1H); ESIMS found for $C_{21}H_{24}N_4O$ m/z 349.2 (M+1).

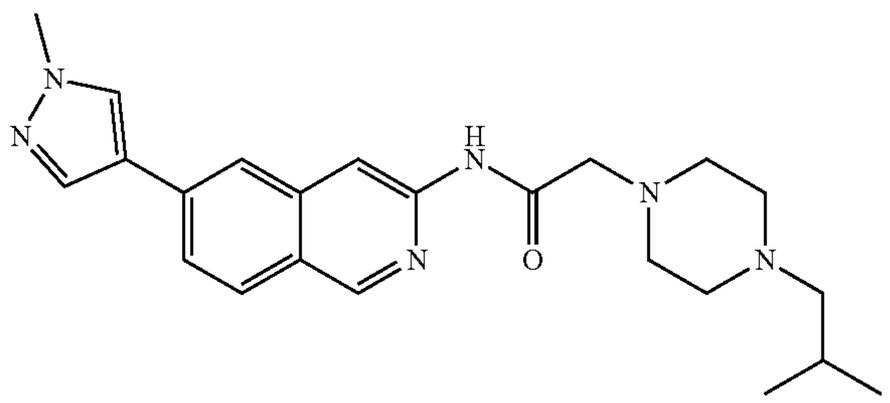
270



N-(6-(1-Methyl-1H-pyrazol-5-yl)isoquinolin-3-yl)-1-(3,3,3-trifluoropropyl) piperidine-4-carboxamide 270

Off-white solid (45.0 mg, 0.104 mmol, 44.9% yield). ^1H NMR (DMSO-d_6, 500 MHz) δ ppm 1.61-1.75 (m, 2H), 1.75-1.86 (m, 2H), 1.98 (br d, J=1.92 Hz, 2H), 2.42-2.63 (m, 5H), 2.95 (br d, J=1.10 Hz, 2H), 3.97 (s, 3H), 6.60 (d, J=1.92 Hz, 1H), 7.54 (d, J=1.92 Hz, 1H), 7.66 (dd, J=8.37, 1.51 Hz, 1H), 8.07 (s, 1H), 8.14 (d, J=8.51 Hz, 1H), 8.58 (s, 1H), 9.18 (s, 1H), 10.60 (s, 1H); ESIMS found for $C_{22}H_{24}F_3N_5O$ m/z 432.2 (M+1).

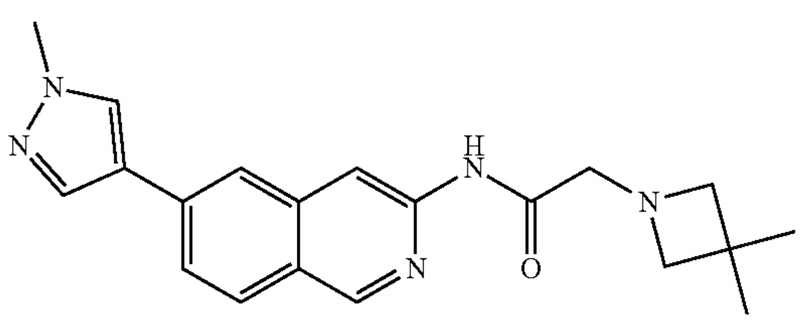
272



2-(4-Isobutylpiperazin-1-yl)-N-[6-(1-methylpyrazol-4-yl)-3-isoquinolyl]acetamide 272

Off-white solid (39.0 mg, 0.096 mmol, 29.1% yield). ^1H NMR (DMSO-d_6, 500 MHz) δ ppm 0.85 (d, J=6.59 Hz, 6H), 1.76 (dquin, J=13.64, 6.81, 6.81, 6.81, 6.81 Hz, 1H), 2.06 (d, J=7.41 Hz, 2H), 2.41 (br s, 4H), 2.58 (br s, 4H), 3.22 (s, 2H), 3.90 (s, 3H), 7.77 (dd, J=8.51, 1.65 Hz, 1H), 8.02 (d, J=8.51 Hz, 1H), 8.10 (s, 2H), 8.37 (s, 1H), 8.43 (s, 1H), 9.04 (s, 1H), 9.92 (s, 1H); ESIMS found for $C_{23}H_{30}N_6O$ m/z 407.2 (M+1).

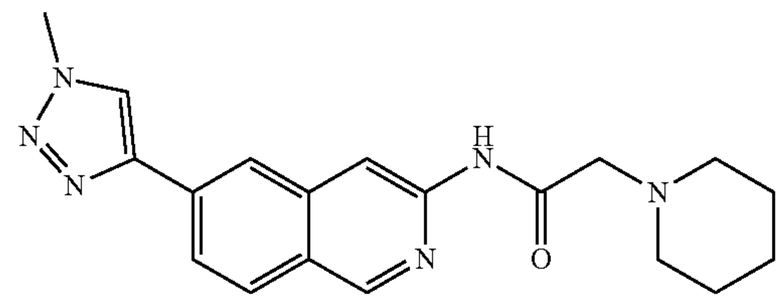
273



2-(3,3-Dimethylazetidin-1-yl)-N-[6-(1-methylpyrazol-4-yl)-3-isoquinolyl]acetamide 273

Off-white solid (51.0 mg, 0.146 mmol, 44.2% yield). ^1H NMR (DMSO-d_6, 500 MHz) δ ppm 1.23 (s, 6H), 3.10 (s, 4H), 3.31 (s, 2H), 3.90 (s, 3H), 7.77 (dd, J=8.51, 1.65 Hz, 1H), 8.02 (d, J=8.51 Hz, 1H), 8.10 (s, 2H), 8.36 (s, 1H), 8.41 (s, 1H), 9.04 (s, 1H), 9.88 (s, 1H); ESIMS found for $C_{20}H_{23}N_5O$ m/z 350.2 (M+1).

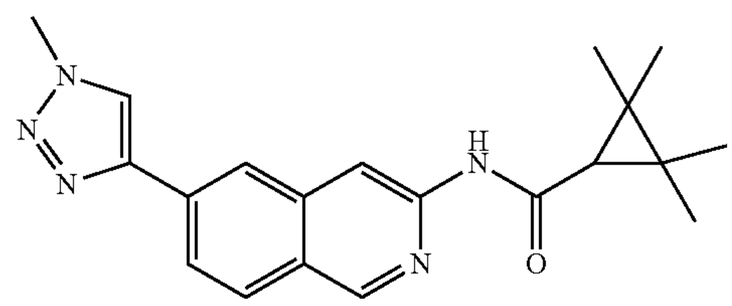
276



N-(6-(1-methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)-2-(piperidin-1-yl) acetamide 276

White solid (61.0 mg, 0.174 mmol, 51.2% yield). ^1H NMR (499 MHz, DMSO-d_6) δ ppm 1.44 (br d, J=5.21 Hz, 2H), 1.59 (quin, J=5.56 Hz, 4H), 2.53 (br s, 4H), 3.18 (s, 2H), 4.14 (s, 3H), 8.04 (dd, J=8.51, 1.65 Hz, 1H), 8.13 (d, J=8.51 Hz, 1H), 8.34 (s, 1H), 8.50 (s, 1H), 8.74 (s, 1H), 9.13 (s, 1H), 9.97 (s, 1H); ESIMS found for $C_{19}H_{22}N_6O$ m/z 351.2 (M+1).

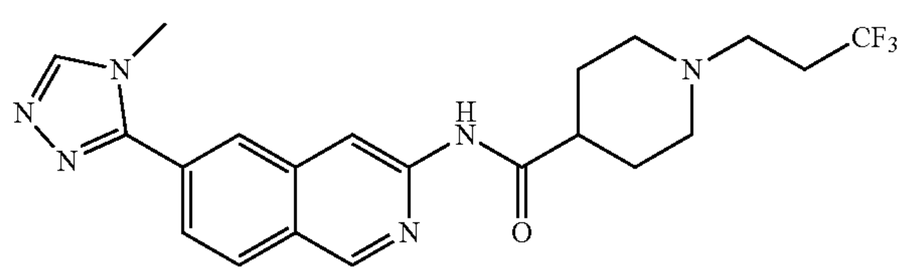
277



2,2,3,3-Tetramethyl-N-(6-(1-methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl) cyclopropane-1-carboxamide 277

White solid (6.0 mg, 0.017 mmol, 6.0% yield). ^1H NMR (499 MHz, DMSO-d_6) δ ppm 1.19 (s, 6H), 1.29 (s, 6H), 1.63 (s, 1H), 4.14 (s, 3H), 7.99 (dd, J=8.51, 1.37 Hz, 1H), 8.09 (d, J=8.51 Hz, 1H), 8.28 (s, 1H), 8.47 (s, 1H), 8.69 (s, 1H), 9.09 (s, 1H), 10.50 (s, 1H); ESIMS found for $C_{20}H_{23}N_5O$ m/z 350.2 (M+1).

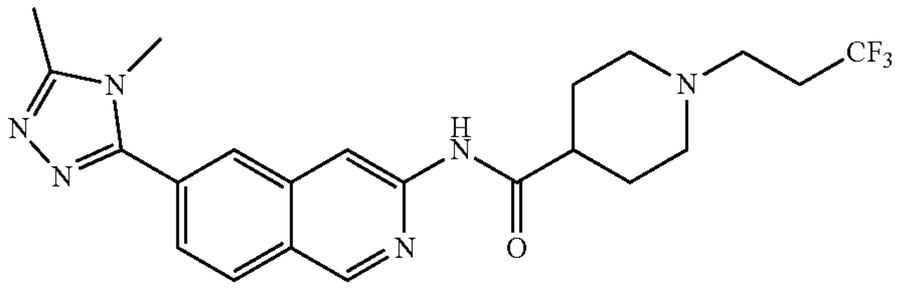
278



N-(6-(4-Methyl-4H-1,2,4-triazol-3-yl)isoquinolin-3-yl)-1-(3,3,3-trifluoropropyl)piperidine-4-carboxamide 278

Off-white solid (30.0 mg, 0.069 mmol, 30.2% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.60-1.74 (m, 2H), 1.80 (br d, J=10.70 Hz, 2H), 1.92-2.03 (m, 2H), 2.40-2.49 (m, 2H), 2.51-2.62 (m, 3H), 2.94 (br d, J=11.25 Hz, 2H), 3.88 (s, 3H), 7.90 (dd, J=8.51, 1.65 Hz, 1H), 8.19 (d, J=8.51 Hz, 1H), 8.27 (s, 1H), 8.63 (s, 1H), 8.65 (s, 1H), 9.22 (s, 1H), 10.63 (s, 1H); ESIMS found for $C_{21}H_{23}F_3N_6O$ m/z 433.2 (M+1).

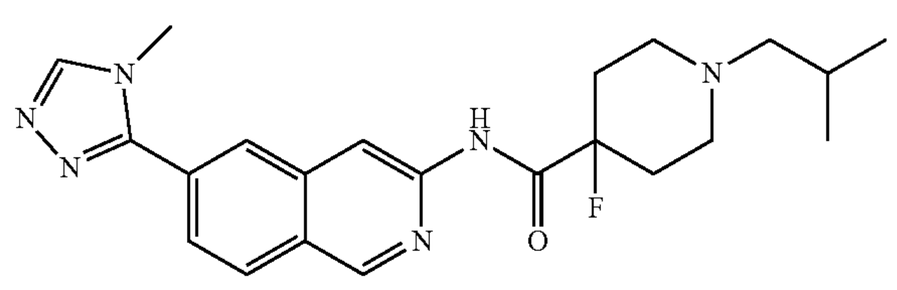
279



N-(6-(4,5-Dimethyl-4H-1,2,4-triazol-3-yl)isoquinolin-3-yl)-1-(3,3,3-trifluoropropyl)piperidine-4-carboxamide 279

Light pink solid (53.0 mg, 0.119 mmol, 51.6% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.62-1.73 (m, 2H), 1.80 (br d, J=11.53 Hz, 2H), 1.92-2.04 (m, 2H), 2.40-2.49 (m, 5H), 2.51-2.61 (m, 3H), 2.94 (br d, J=10.98 Hz, 2H), 3.70 (s, 3H), 7.82 (dd, J=8.51, 1.65 Hz, 1H), 8.14-8.22 (m, 2H), 8.62 (s, 1H), 9.21 (s, 1H), 10.63 (s, 1H); ESIMS found for $C_{22}H_{25}F_3N_6O$ m/z 447.2 (M+1).

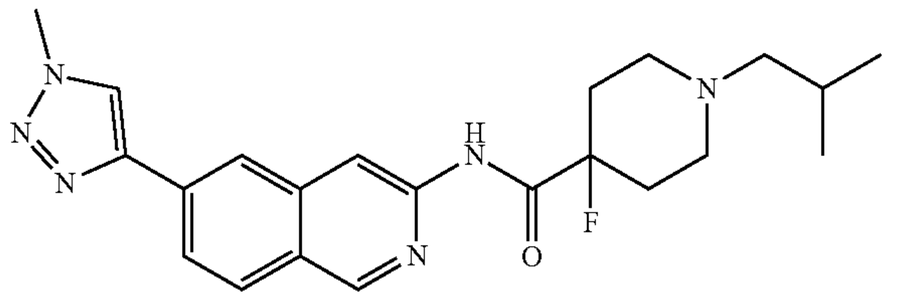
280



4-Fluoro-1-isobutyl-N-(6-(4-methyl-4H-1,2,4-triazol-3-yl)isoquinolin-3-yl) piperidine-4-carboxamide 280

White solid (38.0 mg, 0.093 mmol, 25.2% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 0.88 (d, J=6.59 Hz, 6H), 1.79 (dquin, J=13.46, 6.79, 6.79, 6.79, 6.79 Hz, 1H), 1.92-2.02 (m, 2H), 2.09 (d, J=7.41 Hz, 3H), 2.12-2.21 (m, 3H), 2.74-2.83 (m, 2H), 3.89 (s, 3H), 7.97 (dd, J=8.51, 1.65 Hz, 1H), 8.24 (d, J=8.51 Hz, 1H), 8.36 (s, 1H), 8.60 (s, 1H), 8.66 (s, 1H), 9.28 (s, 1H), 10.06 (d, J=3.84 Hz, 1H); ESIMS found for $C_{22}H_{27}FN_6O$ m/z 411.2 (M+1).

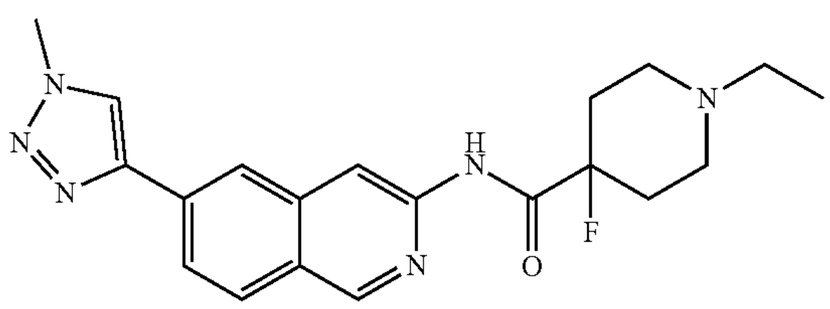
281



4-Fluoro-1-isobutyl-N-(6-(1-methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl) piperidine-4-carboxamide 281

Off-white solid (31.0 mg, 0.076 mmol, 20.6% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 0.88 (d, J=6.59 Hz, 6H), 1.79 (dquin, J=13.52, 6.71, 6.71, 6.71, 6.71 Hz, 1H), 1.91-2.01 (m, 2H), 2.06-2.22 (m, 6H), 2.78 (br d, J=7.96 Hz, 2H), 4.15 (s, 3H), 8.07 (dd, J=8.51, 1.65 Hz, 1H), 8.16 (d, J=8.78 Hz, 1H), 8.37 (s, 1H), 8.47 (s, 1H), 8.74 (s, 1H), 9.17 (s, 1H), 9.95 (d, J=4.12 Hz, 1H); ESIMS found for $C_{22}H_{27}FN_6O$ m/z 411.2 (M+1).

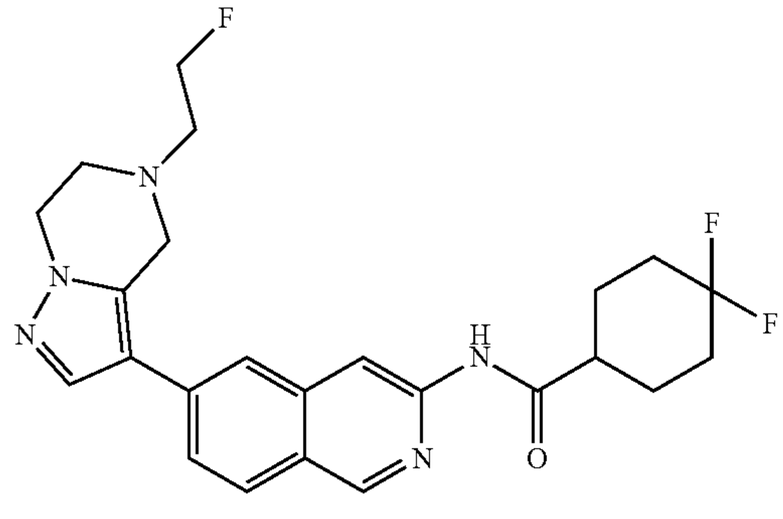
282



1-Ethyl-4-fluoro-N-(6-(1-methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl) piperidine-4-carboxamide 282

Beige solid (6.0 mg, 0.016 mmol, 5.6% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.03 (t, J=7.14 Hz, 3H), 1.93-2.02 (m, 2H), 2.05-2.13 (m, 1H), 2.13-2.20 (m, 3H), 2.39 (q, J=7.14 Hz, 2H), 2.80-2.88 (m, 2H), 4.15 (s, 3H), 8.03-8.10 (m, 1H), 8.16 (d, J=8.51 Hz, 1H), 8.36 (s, 1H), 8.47 (s, 1H), 8.73 (s, 1H), 9.17 (s, 1H), 9.94 (d, J=4.12 Hz, 1H); ESIMS found for $C_{20}H_{23}FN_6O$ m/z 383.2 (M+1).

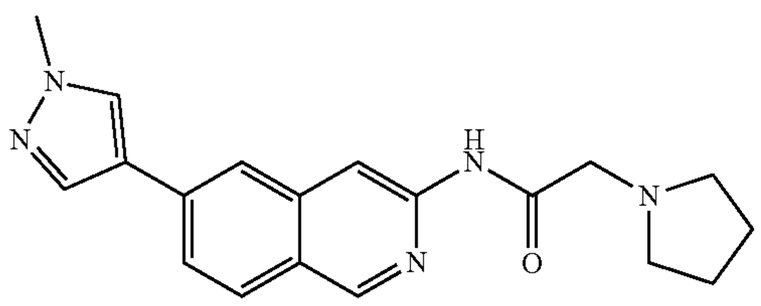
283



4,4-Difluoro-N-(6-(5-(2-fluoroethyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-3-yl)isoquinolin-3-yl) cyclohexane-1-carboxamide 283

Beige solid (7.7 mg, 0.017 mmol, 12.4% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.66-1.77 (m, 2H), 1.77-1.91 (m, 2H), 1.92-2.01 (m, 2H), 2.08-2.19 (m, 2H), 2.67-2.76 (m, 1H), 2.96 (t, J=4.80 Hz, 1H), 3.01 (t, J=4.80 Hz, 1H), 3.07 (t, J=5.35 Hz, 2H), 4.08 (s, 2H), 4.18 (t, J=5.35 Hz, 2H), 4.66 (dt, J=47.85, 4.95 Hz, 2H), 7.64 (dd, J=8.51, 1.37 Hz, 1H), 7.76 (s, 1H), 8.00 (s, 1H), 8.03 (d, J=8.78 Hz, 1H), 8.47 (s, 1H), 9.06 (s, 1H), 10.58 (s, 1H); ESIMS found for $C_{24}H_{26}F_3N_5O$ m/z 458.2 (M+1).

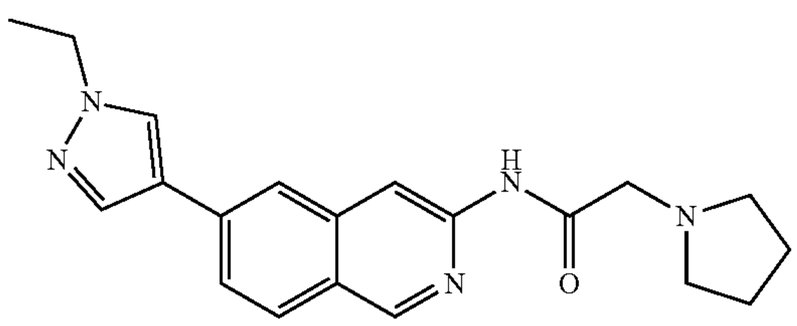
284



N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(pyrrolidin-1-yl) acetamide 284

White gummy paste (53.0 mg, 0.150 mmol, 45.5% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.78 (dt, J=6.52, 3.19 Hz, 4H), 2.66 (br t, J=5.90 Hz, 4H), 3.35 (s, 2H), 3.90 (s, 3H), 7.77 (dd, J=8.51, 1.65 Hz, 1H), 8.02 (d, J=8.51 Hz, 1H), 8.10 (s, 2H), 8.37 (s, 1H), 8.43 (s, 1H), 9.03 (s, 1H), 9.92 (s, 1H); ESIMS found for $C_{19}H_{21}N_5O$ m/z 336.2 (M+1).

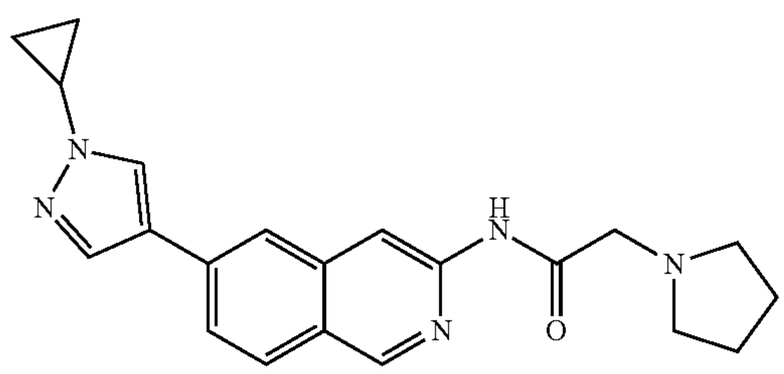
285



N-(6-(1-Ethyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(pyrrolidin-1-yl) acetamide 285

Dark pink paste (42.0 mg, 0.114 mmol, 63.6% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.44 (t, J=7.27 Hz, 3H), 1.78 (dt, J=6.66, 3.12 Hz, 4H), 2.62-2.69 (m, 4H), 3.35 (s, 2H), 4.18 (q, J=7.41 Hz, 2H), 7.78 (dd, J=8.51, 1.65 Hz, 1H), 8.02 (d, J=8.51 Hz, 1H), 8.09-8.14 (m, 2H), 8.43 (s, 2H), 9.03 (s, 1H), 9.92 (s, 1H); ESIMS found for $C_{20}H_{23}N_5O$ m/z 350.2 (M+1).

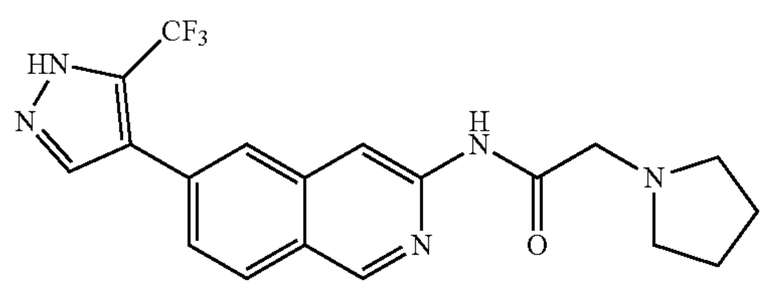
286



N-(6-(1-Cyclopropyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(pyrrolidin-1-yl) acetamide 286

White paste (68.0 mg, 0.179 mmol, 59.7% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 0.98-1.05 (m, 2H), 1.08-1.13 (m, 2H), 1.78 (dt, J=6.86, 3.16 Hz, 4H), 2.62-2.69 (m, 4H), 3.35 (s, 2H), 3.78 (tt, J=7.34, 3.77 Hz, 1H), 7.79 (dd, J=8.51, 1.65 Hz, 1H), 8.01 (d, J=8.78 Hz, 1H), 8.08-8.15 (m, 2H), 8.43 (s, 1H), 8.48 (s, 1H), 9.03 (s, 1H), 9.92 (s, 1H); ESIMS found for $C_{21}H_{23}N_5O$ m/z 362.2 (M+1).

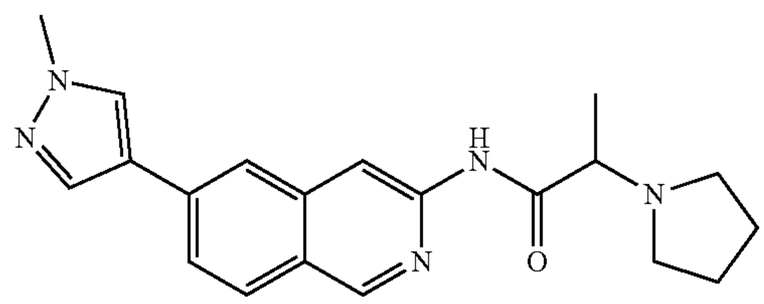
287



2-(Pyrrolidin-1-yl)-N-(6-(5-(trifluoromethyl)-1H-pyrazol-4-yl)isoquinolin-3-yl)acetamide 287

White solid (83.0 mg, 0.203 mmol, 45.1% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.78 (dt, J=6.72, 3.22 Hz, 4H), 2.61-2.70 (m, 4H), 3.36 (s, 2H), 7.60 (dd, J=8.37, 1.24 Hz, 1H), 7.93 (s, 1H), 8.12 (d, J=8.51 Hz, 1H), 8.40 (s, 1H), 8.46 (s, 1H), 9.14 (s, 1H), 10.01 (s, 1H); ESIMS found for $C_{19}H_{18}F_3N_5O$ m/z 390.1 (M+1).

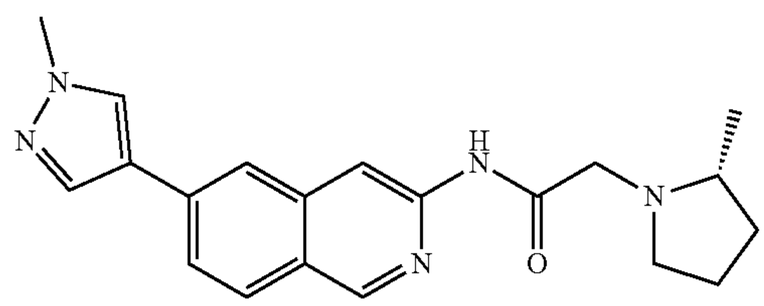
288



N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(pyrrolidin-1-yl) propanamide 288

White solid (58.8 mg, 0.158 mmol, 50.9% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.30 (d, J=6.86 Hz, 3H), 1.74 (br s, 4H), 2.57-2.69 (m, 4H), 3.28 (q, J=6.95 Hz, 1H), 3.90 (s, 3H), 7.76 (dd, J=8.51, 1.65 Hz, 1H), 8.02 (d, J=8.51 Hz, 1H), 8.06-8.12 (m, 2H), 8.36 (s, 1H), 8.43 (s, 1H), 9.03 (s, 1H), 9.95 (s, 1H); ESIMS found for $C_{20}H_{23}N_5O$ m/z 350.1 (M+1).

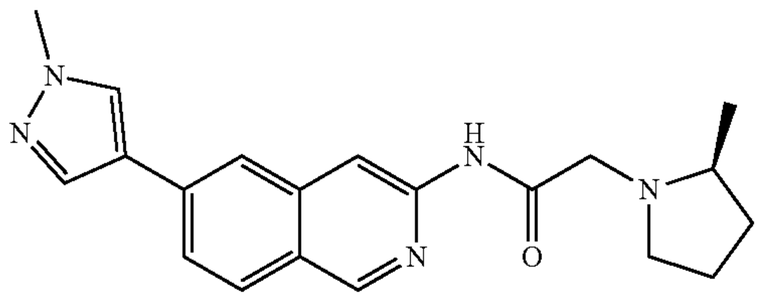
289



(R)—N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(2-methylpyrrolidin-1-yl)acetamide 289

White paste (79.5 mg, 0.216 mmol, 65.5% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.09 (d, J=6.04 Hz, 3H), 1.42 (dddd, J=12.25, 10.33, 8.30, 6.45 Hz, 1H), 1.66-1.83 (m, 2H), 1.91-2.02 (m, 1H), 2.40 (q, J=8.78 Hz, 1H), 2.56-2.66 (m, 1H), 3.12 (d, J=16.19 Hz, 1H), 3.14-3.19 (m, 1H), 3.54 (d, J=16.47 Hz, 1H), 3.90 (s, 3H), 7.77 (dd, J=8.51, 1.65 Hz, 1H), 8.02 (d, J=8.51 Hz, 1H), 8.07-8.14 (m, 2H), 8.37 (s, 1H), 8.44 (s, 1H), 9.03 (s, 1H), 9.89 (s, 1H); ESIMS found for $C_{20}H_{23}N_5O$ m/z 350.2 (M+1).

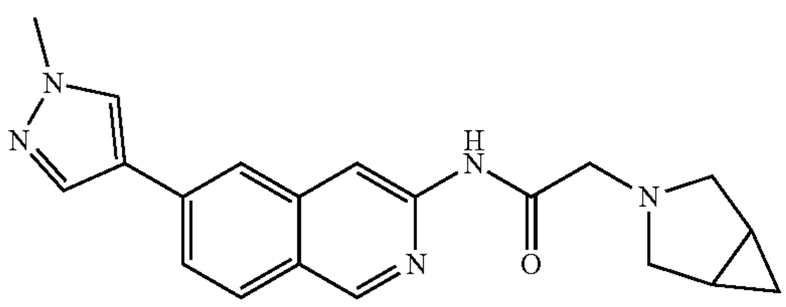
290



(S)—N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(2-methylpyrrolidin-1-yl)acetamide 290

White solid (77.0 mg, 0.209 mmol, 66.3% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.09 (d, J=6.04 Hz, 3H), 1.42 (dddd, J=12.32, 10.39, 8.30, 6.31 Hz, 1H), 1.66-1.84 (m, 2H), 1.91-2.01 (m, 1H), 2.40 (q, J=8.78 Hz, 1H), 2.57-2.66 (m, 1H), 3.12 (d, J=16.47 Hz, 1H), 3.14-3.19 (m, 1H), 3.54 (d, J=16.19 Hz, 1H), 3.90 (s, 3H), 7.77 (dd, J=8.51, 1.37 Hz, 1H), 8.02 (d, J=8.51 Hz, 1H), 8.08-8.13 (m, 2H), 8.37 (s, 1H), 8.44 (s, 1H), 9.03 (s, 1H), 9.88 (s, 1H); ESIMS found for $C_{20}H_{23}N_5O$ m/z 350.2 (M+1).

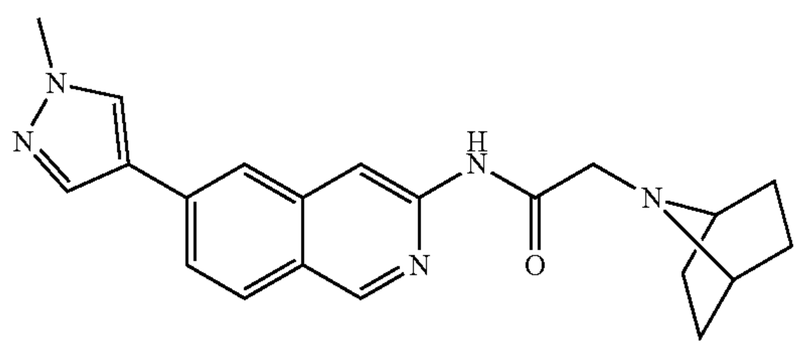
291



2-(3-Azabicyclo[3.1.0]hexan-3-yl)-N-(6-(1-methyl-1H-pyrazol-4-yl) isoquinolin-3-yl)acetamide 291

White solid (72.0 mg, 0.207 mmol, 62.8% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 0.44 (td, J=7.55, 4.12 Hz, 1H), 0.70 (q, J=3.84 Hz, 1H), 1.40-1.48 (m, 2H), 2.57 (br d, J=8.23 Hz, 2H), 3.04 (d, J=8.78 Hz, 2H), 3.33 (s, 2H), 3.90 (s, 3H), 7.77 (dd, J=8.51, 1.37 Hz, 1H), 8.02 (d, J=8.51 Hz, 1H), 8.09 (s, 2H), 8.36 (s, 1H), 8.41 (s, 1H), 9.03 (s, 1H), 9.77 (s, 1H); ESIMS found for $C_{20}H_{21}N_5O$ m/z 348.2 (M+1).

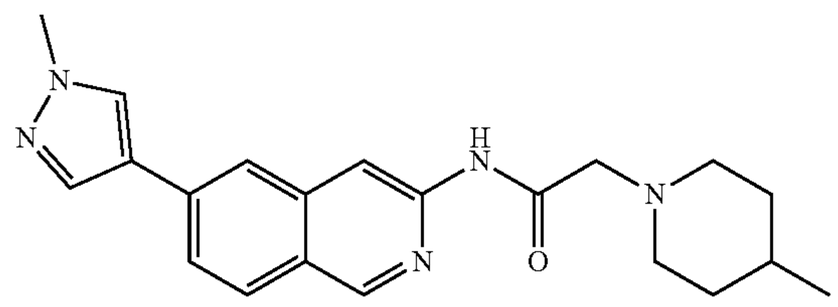
292



2-(7-Azabicyclo[2.2.1]heptan-7-yl)-N-(6-(1-methyl-1H-pyrazol-4-yl) isoquinolin-3-yl)acetamide 292

Beige solid (64.0 mg, 0.177 mmol, 53.7% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.34 (br d, J=6.86 Hz, 4H), 1.74 (br d, J=6.59 Hz, 4H), 3.19 (s, 2H), 3.34-3.39 (m, 2H), 3.90 (s, 3H), 7.74-7.83 (m, 1H), 8.02 (d, J=8.78 Hz, 1H), 8.08-8.14 (m, 2H), 8.37 (s, 1H), 8.46 (s, 1H), 9.04 (s, 1H), 10.08 (s, 1H); ESIMS found for $C_{21}H_{23}N_5O$ m/z 362.2 (M+1).

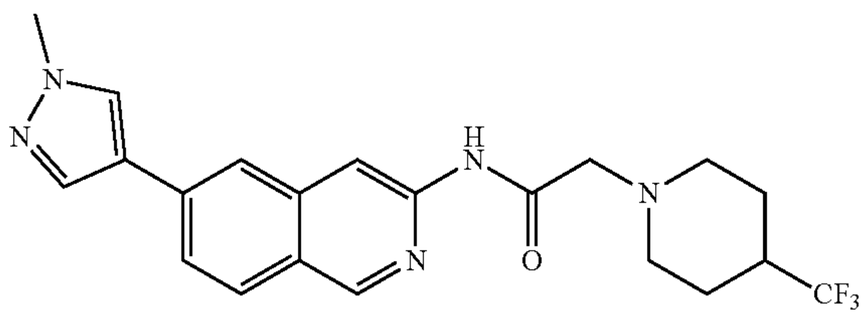
293



N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(4-methylpiperidin-1-yl)acetamide 293

White solid (56.0 mg, 0.146 mmol, 44.4% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 0.93 (d, J=6.59 Hz, 3H), 1.18-1.29 (m, 2H), 1.32-1.43 (m, 1H), 1.64 (br d, J=11.25 Hz, 2H), 2.20 (td, J=11.53, 1.92 Hz, 2H), 2.87 (br d, J=11.53 Hz, 2H), 3.18 (s, 2H), 3.90 (s, 3H), 7.77 (dd, J=8.51, 1.37 Hz, 1H), 8.02 (d, J=8.51 Hz, 1H), 8.10 (s, 2H), 8.37 (s, 1H), 8.43 (s, 1H), 9.04 (s, 1H), 9.90 (s, 1H); ESIMS found for $C_{21}H_{25}N_5O$ m/z 364.2 (M+1).

294

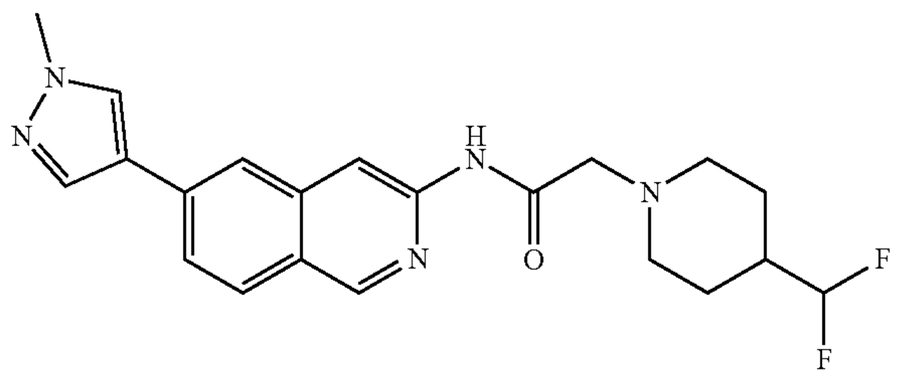


N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(4-(trifluoromethyl) piperidin-1-yl)acetamide 294

Off-white solid (92.0 mg, 0.209 mmol, 63.4% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.56 (qd, J=12.44, 3.84 Hz, 2H), 1.83 (br d, J=12.62 Hz, 2H), 2.28 (td, J=11.94, 1.92 Hz, 2H), 2.30-2.39 (m, 1H), 3.00 (br d, J=11.53 Hz, 2H),

3.25 (s, 2H), 3.90 (s, 3H), 7.77 (dd, J=8.64, 1.51 Hz, 1H), 8.02 (d, J=8.51 Hz, 1H), 8.10 (s, 2H), 8.37 (s, 1H), 8.44 (s, 1H), 9.04 (s, 1H), 9.98 (s, 1H); ESIMS found for $C_{21}H_{22}F_3N_5O$ m/z 418.2 (M+1).

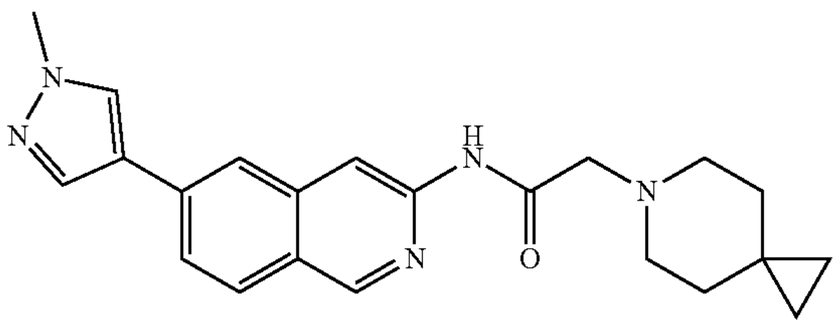
295



2-(4-(Difluoromethyl)piperidin-1-yl)-N-(6-(1-methyl-1H-pyrazol-4-yl) isoquinolin-3-yl)acetamide 295

Beige solid (70.0 mg, 0.167 mmol, 62.4% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.47 (qd, J=12.44, 3.84 Hz, 2H), 1.71 (br d, J=12.35 Hz, 2H), 1.75-1.90 (m, 1H), 2.23 (td, J=11.80, 1.92 Hz, 2H), 2.97 (br d, J=11.53 Hz, 2H), 3.23 (s, 2H), 3.90 (s, 3H), 5.95 (td, J=56.90, 4.40 Hz, 1H), 7.77 (dd, J=8.51, 1.37 Hz, 1H), 8.02 (d, J=8.51 Hz, 1H), 8.10 (s, 2H), 8.37 (s, 1H), 8.44 (s, 1H), 9.04 (s, 1H), 9.93 (s, 1H); ESIMS found for $C_{21}H_{23}F_2N_5O$ m/z 400.2 (M+1).

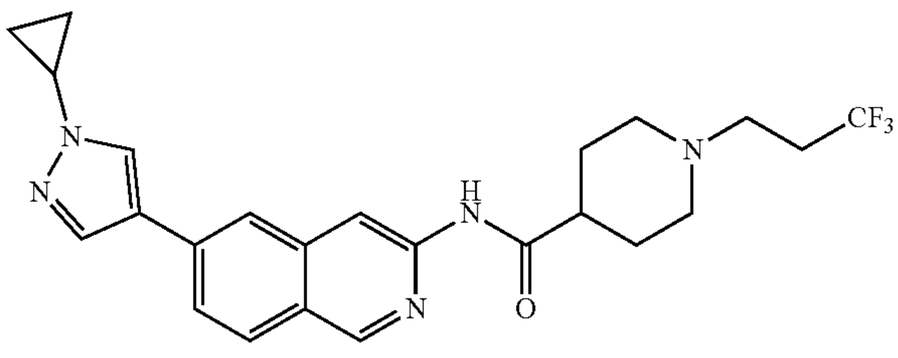
296



N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(6-azaspiro[2.5]octan-6-yl)acetamide 296

Off-white solid (60.0 mg, 0.152 mmol, 56.9% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 0.29 (s, 4H), 1.42 (br s, 4H), 2.56-2.64 (m, 4H), 3.24 (s, 2H), 3.90 (s, 3H), 7.77 (dd, J=8.64, 1.51 Hz, 1H), 8.02 (d, J=8.51 Hz, 1H), 8.08-8.14 (m, 2H), 8.37 (s, 1H), 8.44 (s, 1H), 9.04 (s, 1H), 9.96 (s, 1H); ESIMS found for $C_{22}H_{25}N_5O$ m/z 376.2 (M+1).

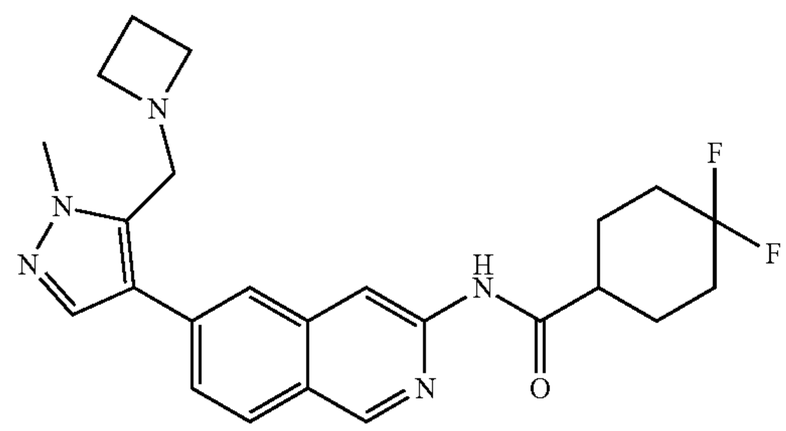
297



N-(6-(1-Cyclopropyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-1-(3,3,3-trifluoropropyl)piperidine-4-carboxamide 297

Off-white solid (21.0 mg, 0.046 mmol, 24.7% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 0.97-1.06 (m, 2H), 1.08-1.14 (m, 2H), 1.60-1.73 (m, 2H), 1.79 (br d, J=10.43 Hz, 2H), 1.92-2.02 (m, 2H), 2.40-2.60 (m, 5H), 2.93 (br d, J=11.25 Hz, 2H), 3.78 (tt, J=7.44, 3.81 Hz, 1H), 7.76 (dd, J=8.51, 1.37 Hz, 1H), 7.99 (d, J=8.51 Hz, 1H), 8.04-8.11 (m, 2H), 8.45 (d, J=9.06 Hz, 2H), 9.02 (s, 1H), 10.47 (s, 1H); ESIMS found for $C_{24}H_{26}F_3N_5O$ m/z 458.2 (M+1).

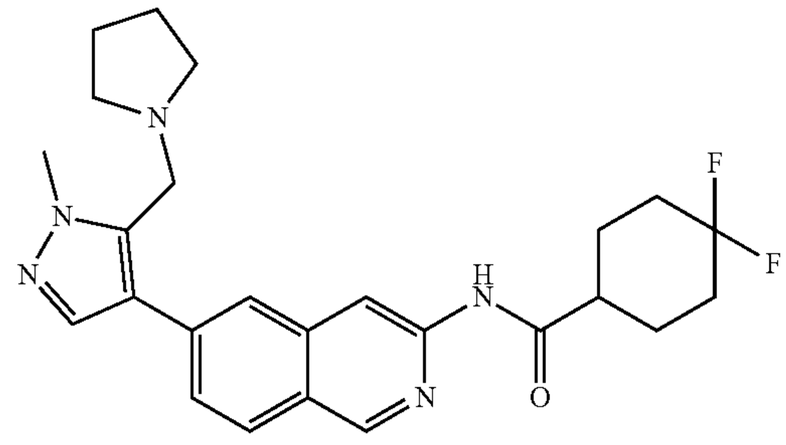
298



N-(6-(5-(Azetidin-1-ylmethyl)-1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-4,4-difluorocyclohexane-1-carboxamide 298

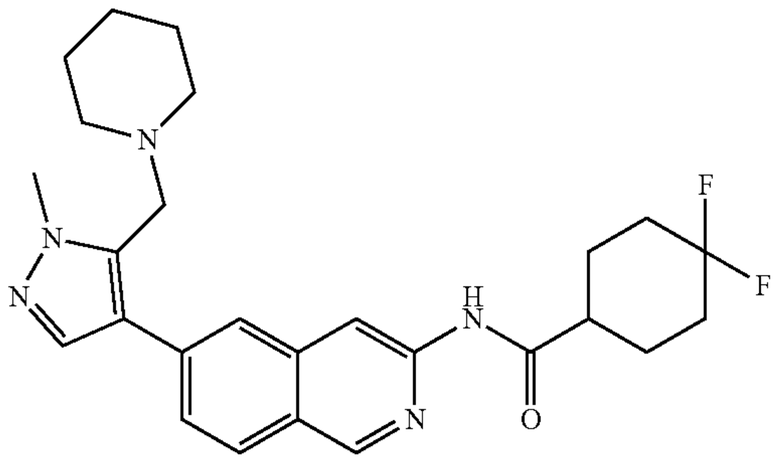
Beige solid (4.4 mg, 0.010 mmol, 3.6% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.67-2.02 (m, 8H), 2.07-2.19 (m, 2H), 2.67-2.77 (m, 1H), 3.11 (t, J=6.86 Hz, 4H), 3.77 (s, 2H), 3.92 (s, 3H), 7.67 (dd, J=8.51, 1.37 Hz, 1H), 7.75 (s, 1H), 7.93 (s, 1H), 8.05 (d, J=8.51 Hz, 1H), 8.46 (s, 1H), 9.09 (s, 1H), 10.60 (s, 1H); ESIMS found for $C_{24}H_{27}F_2N_5O$ m/z 440.2 (M+1).

299



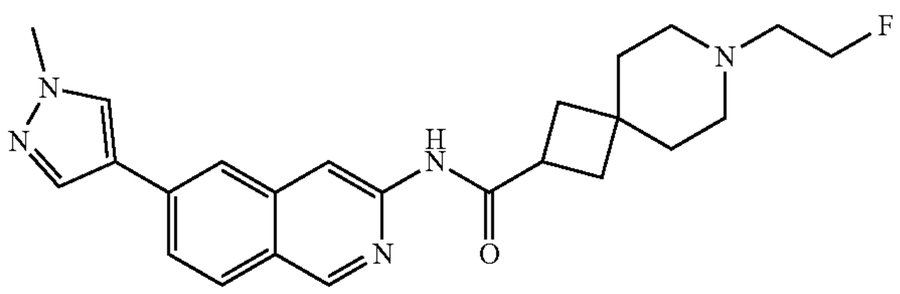
4,4-Difluoro-N-(6-(1-methyl-5-(pyrrolidin-1-ylmethyl)-1H-pyrazol-4-yl) isoquinolin-3-yl)cyclohexane-1-carboxamide 299

Beige solid (26.4 mg, 0.058 mmol, 23.2% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.67 (br s, 4H), 1.69-1.91 (m, 4H), 1.95 (br d, J=12.90 Hz, 2H), 2.06-2.18 (m, 2H), 2.44 (br s, 4H), 2.71 (br t, J=10.84 Hz, 1H), 3.83 (s, 2H), 3.92 (s, 3H), 7.68 (dd, J=8.51, 1.65 Hz, 1H), 7.78 (s, 1H), 7.96 (s, 1H), 8.03 (d, J=8.51 Hz, 1H), 8.44 (s, 1H), 9.08 (s, 1H), 10.59 (s, 1H); ESIMS found for $C_{25}H_{29}F_2N_5O$ m/z 454.2 (M+1).



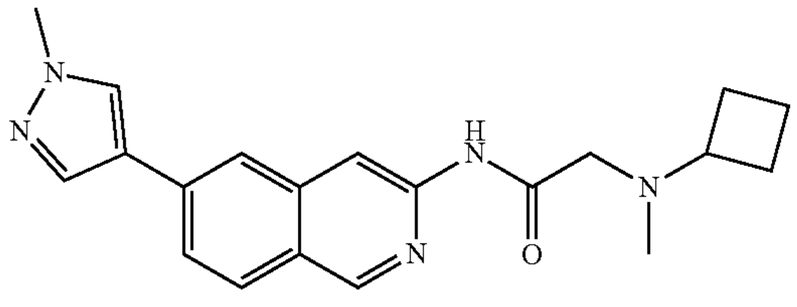
4,4-Difluoro-N-(6-(1-methyl-5-(piperidin-1-ylmethyl)-1H-pyrazol-4-yl) isoquinolin-3-yl)cyclohexane-1-carboxamide 300

White solid (10.6 mg, 0.023 mmol, 18.1% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.38 (br d, J=4.12 Hz, 2H), 1.44-1.53 (m, 4H), 1.66-1.90 (m, 4H), 1.92-2.01 (m, 2H), 2.06-2.18 (m, 2H), 2.36 (br d, J=1.65 Hz, 4H), 2.65-2.76 (m, 1H), 3.65 (s, 2H), 3.91 (s, 3H), 7.70 (dd, J=8.51, 1.65 Hz, 1H), 7.80 (s, 1H), 7.98-8.07 (m, 2H), 8.45 (s, 1H), 9.08 (s, 1H), 10.58 (s, 1H); ESIMS found for $C_{26}H_{31}F_2N_5O$ m/z 468.2 (M+1).



7-(2-Fluoroethyl)-N-(6-(1-methyl-1H-pyrazol-4-yl) isoquinolin-3-yl)-7-azaspiro[3.5]nonane-2-carboxamide 301

Beige solid (50.0 mg, 0.119 mmol, 18.1% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.53 (br t, J=5.35 Hz, 2H), 1.59 (br t, J=5.35 Hz, 2H), 1.97 (d, J=8.51 Hz, 4H), 2.30 (br s, 2H), 2.33-2.44 (m, 2H), 2.55 (dt, J=28.30, 5.20 Hz, 2H), 3.33-3.42 (m, 1H), 3.90 (s, 3H), 4.50 (dt, J=48.10, 5.25 Hz, 2H), 7.74 (dd, J=8.51, 1.65 Hz, 1H), 7.99 (d, J=8.51 Hz, 1H), 8.03 (s, 1H), 8.08 (s, 1H), 8.35 (s, 1H), 8.46 (s, 1H), 9.01 (s, 1H), 10.34 (s, 1H); ESIMS found for $C_{24}H_{28}FN_5O$ m/z 422.2 (M+1).



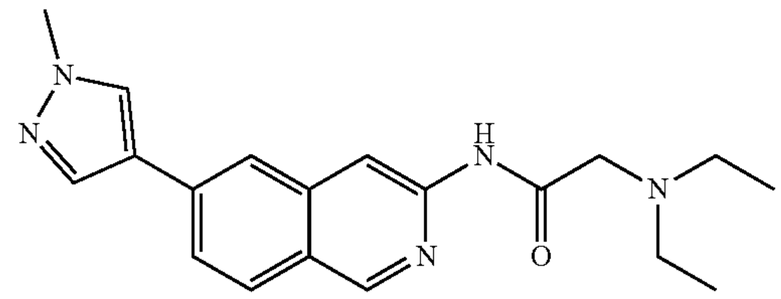
N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(methylamino)-2-(1-methylcyclobutyl)acetamide 302

300

2-(Cyclobutyl(methyl)amino)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)acetamide 302

Off-white solid (69.0 mg, 0.198 mmol, 59.8% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.53-1.69 (m, 2H), 1.81-1.92 (m, 2H), 1.97-2.07 (m, 2H), 2.23 (s, 3H), 3.03-3.10 (m, 1H), 3.11 (s, 2H), 3.90 (s, 3H), 7.77 (dd, J=8.51, 1.37 Hz, 1H), 8.03 (d, J=8.51 Hz, 1H), 8.08-8.14 (m, 2H), 8.37 (s, 1H), 8.43 (s, 1H), 9.04 (s, 1H), 9.91 (s, 1H); ESIMS found for $C_{20}H_{23}N_5O$ m/z 350.2 (M+1).

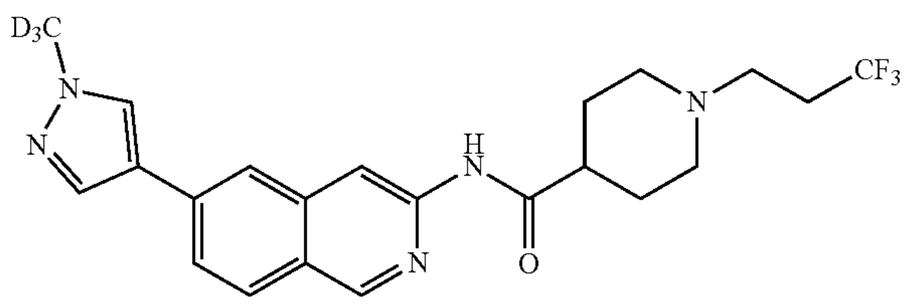
303



2-(Diethylamino)-N-(6-(1-methyl-1H-pyrazol-4-yl) isoquinolin-3-yl) acetamide 303

White paste (74.0 mg, 0.219 mmol, 66.5% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.05 (t, J=7.14 Hz, 6H), 2.65 (q, J=7.14 Hz, 4H), 3.24 (s, 2H), 3.90 (s, 3H), 7.77 (dd, J=8.51, 1.37 Hz, 1H), 8.02 (d, J=8.51 Hz, 1H), 8.08-8.14 (m, 2H), 8.37 (s, 1H), 8.43 (s, 1H), 9.03 (s, 1H), 9.93 (s, 1H); ESIMS found for $C_{19}H_{23}N_5O$ m/z 338.2 (M+1).

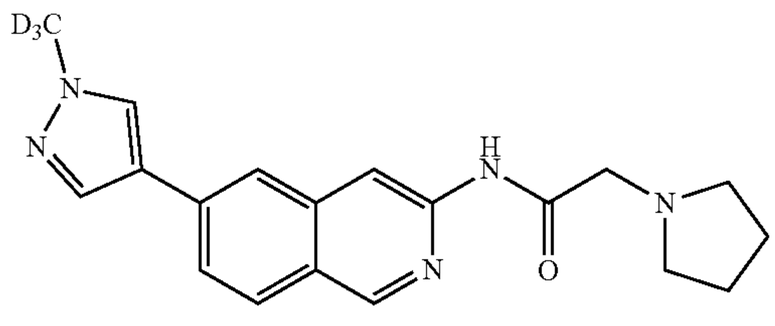
304



N-(6-(1-(Methyl-d3)-1H-pyrazol-4-yl)isoquinolin-3-yl)-1-(3,3,3-trifluoropropyl)piperidine-4-carboxamide 304

Off-white solid (54.0 mg, 0.124 mmol, 44.6% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.60-1.72 (m, 2H), 1.79 (br d, J=10.15 Hz, 2H), 1.91-2.02 (m, 2H), 2.39-2.60 (m, 5H), 2.93 (br d, J=11.25 Hz, 2H), 7.74 (dd, J=8.51, 1.65 Hz, 1H), 8.00 (d, J=8.51 Hz, 1H), 8.03 (s, 1H), 8.07 (s, 1H), 8.34 (s, 1H), 8.44 (s, 1H), 9.02 (s, 1H), 10.47 (s, 1H); ESIMS found for $C_{22}H_{21}D_3F_3N_5O$ m/z 435.2 (M+1).

305

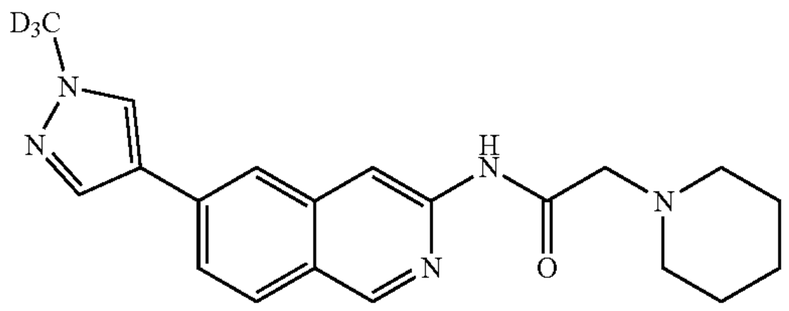


N-(6-(1-(Methyl-d3)-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(pyrrolidin-1-yl)acetamide 305

N-(6-(1-(Methyl-d3)-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(pyrrolidin-1-yl) acetamide 305

White paste (80.0 mg, 0.236 mmol, 71.6% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.78 (dt, J=6.59, 3.29 Hz, 4H), 2.62-2.70 (m, 4H), 3.35 (s, 2H), 7.77 (dd, J=8.51, 1.65 Hz, 1H), 8.02 (d, J=8.51 Hz, 1H), 8.10 (s, 2H), 8.36 (s, 1H), 8.43 (s, 1H), 9.03 (s, 1H), 9.92 (s, 1H); ESIMS found for $C_{19}H_{18}D_3N_5O$ m/z 339.2 (M+1).

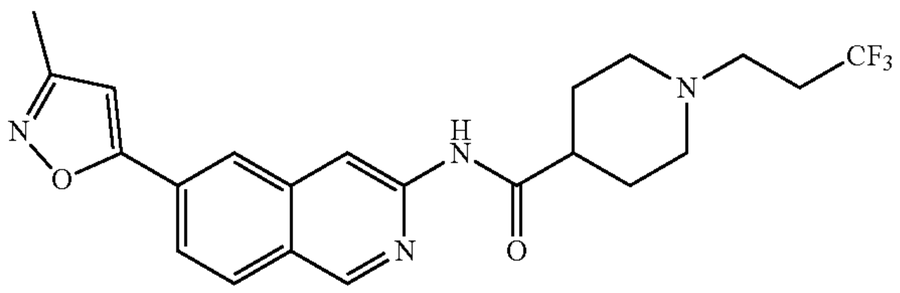
306



N-(6-(1-(Methyl-d3)-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(piperidin-1-yl) acetamide 306

Beige solid (82.0 mg, 0.233 mmol, 70.5% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.43 (br d, J=4.94 Hz, 2H), 1.59 (quin, J=5.56 Hz, 4H), 2.52 (br d, J=1.92 Hz, 4H), 3.17 (s, 2H), 7.77 (dd, J=8.51, 1.65 Hz, 1H), 8.02 (d, J=8.78 Hz, 1H), 8.10 (s, 2H), 8.36 (s, 1H), 8.43 (s, 1H), 9.04 (s, 1H), 9.91 (s, 1H); ESIMS found for $C_{20}H_{20}D_3N_5O$ m/z 353.2 (M+1).

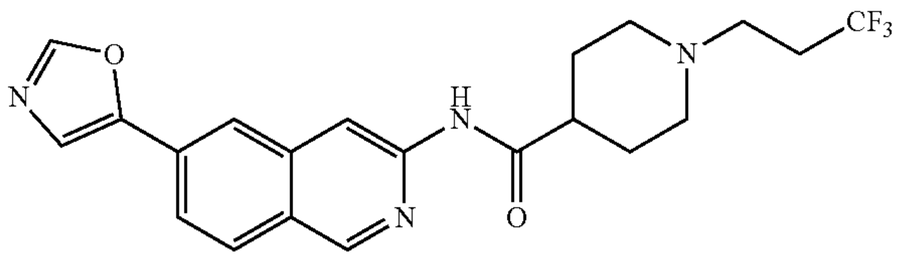
307



N-(6-(3-Methylisoxazol-5-yl)isoquinolin-3-yl)-1-(3,3,3-trifluoropropyl) piperidine-4-carboxamide 307

White solid (3.0 mg, 0.007 mmol, 2.4% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.61-1.73 (m, 2H), 1.80 (br d, J=10.43 Hz, 2H), 1.92-2.02 (m, 2H), 2.41-2.61 (m, 5H), 2.51 (s, 3H), 2.93 (br d, J=11.25 Hz, 2H), 7.68 (dd, J=8.37, 1.51 Hz, 1H), 8.04 (s, 1H), 8.11 (d, J=8.51 Hz, 1H), 8.54 (s, 1H), 9.13 (s, 1H), 9.34 (s, 1H), 10.56 (s, 1H); ESIMS found for $C_{22}H_{23}F_3N_4O_2$ m/z 433.2 (M+1).

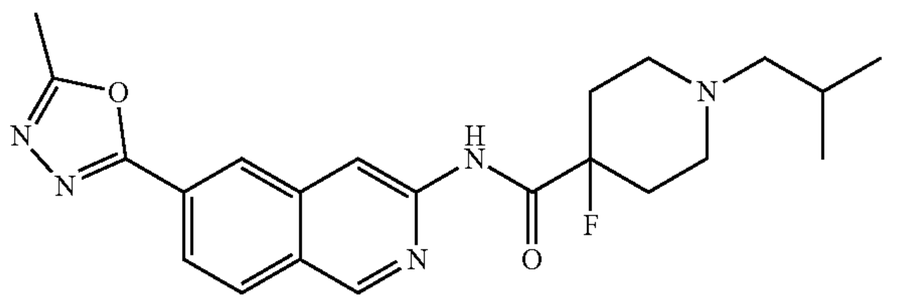
308



N-(6-(Oxazol-5-yl)isoquinolin-3-yl)-1-(3,3,3-trifluoropropyl)piperidine-4-carboxamide 308

Off-white solid (16.0 mg, 0.038 mmol, 16.5% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.58-1.72 (m, 2H), 1.80 (br d, J=10.70 Hz, 2H), 1.91-2.03 (m, 2H), 2.40-2.61 (m, 5H), 2.94 (br d, J=11.25 Hz, 2H), 7.87 (dd, J=8.64, 1.51 Hz, 1H), 7.95 (s, 1H), 8.13 (d, J=8.51 Hz, 1H), 8.20 (s, 1H), 8.54 (s, 1H), 8.58 (s, 1H), 9.13 (s, 1H), 10.58 (s, 1H); ESIMS found for $C_{21}H_{21}F_3N_4O_2$ m/z 419.1 (M+1).

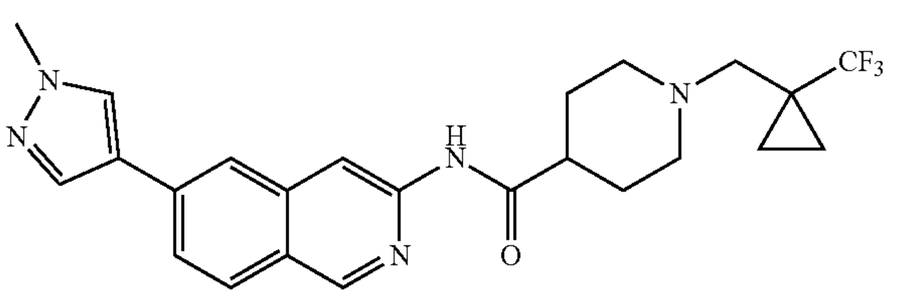
309



4-Fluoro-1-isobutyl-N-(6-(5-methyl-1,3,4-oxadiazol-2-yl)isoquinolin-3-yl) piperidine-4-carboxamide 309

Off-white solid (20.0 mg, 0.049 mmol, 13.2% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 0.88 (d, J=6.59 Hz, 6H), 1.80 (dquin, J=13.55, 6.84, 6.84, 6.84, 6.84 Hz, 1H), 1.92-2.02 (m, 2H), 2.09 (d, J=7.41 Hz, 2H), 2.06-2.21 (m, 4H), 2.64 (s, 3H), 2.75-2.82 (m, 2H), 8.11 (dd, J=8.51, 1.65 Hz, 1H), 8.29 (d, J=8.51 Hz, 1H), 8.57 (s, 1H), 8.60 (s, 1H), 9.30 (s, 1H), 10.11 (d, J=3.57 Hz, 1H); ESIMS found for $C_{22}H_{26}FN_5O_2$ m/z 412.2 (M+1).

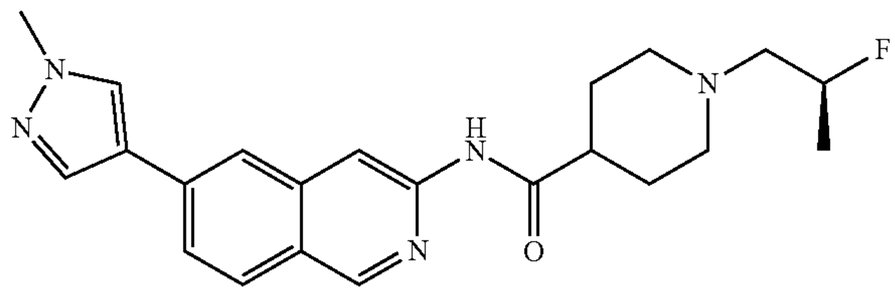
310



N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-1-((1-(trifluoromethyl) cyclopropyl)methyl)piperidine-4-carboxamide 310

Off-white solid (70.0 mg, 0.153 mmol, 76.5% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 0.73 (s, 2H), 0.93-0.99 (m, 2H), 1.60-1.72 (m, 2H), 1.73-1.82 (m, 2H), 1.89-2.00 (m, 2H), 2.49 (br s, 2H), 2.52-2.58 (m, 1H), 2.96 (br d, J=11.25 Hz, 2H), 3.90 (s, 3H), 7.74 (dd, J=8.51, 1.65 Hz, 1H), 8.00 (d, J=8.51 Hz, 1H), 8.04 (s, 1H), 8.08 (s, 1H), 8.35 (s, 1H), 8.44 (s, 1H), 9.02 (s, 1H), 10.46 (s, 1H); ESIMS found for $C_{24}H_{26}F_3N_5O$ m/z 458.2 (M+1).

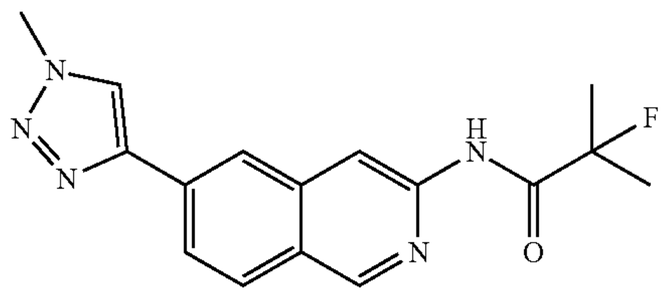
311



(S)-1-(2-Fluoropropyl)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl) piperidine-4-carboxamide 311

White solid (71.0 mg, 0.180 mmol, 60.2% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.26 (dd, J=23.95, 6.35 Hz, 3H), 1.62-1.72 (m, 2H), 1.74-1.82 (m, 2H), 2.00-2.12 (m, 2H), 2.34-2.49 (m, 2H), 2.52-2.59 (m, 1H), 2.93 (br t, J=11.80 Hz, 2H), 3.90 (s, 3H), 4.75-4.94 (m, 1H), 7.74 (dd, J=8.51, 1.65 Hz, 1H), 8.00 (d, J=8.78 Hz, 1H), 8.04 (s, 1H), 8.07 (s, 1H), 8.34 (s, 1H), 8.44 (s, 1H), 9.02 (s, 1H), 10.45 (s, 1H); ESIMS found for $C_{22}H_{26}FN_5O$ m/z 396.2 (M+1).

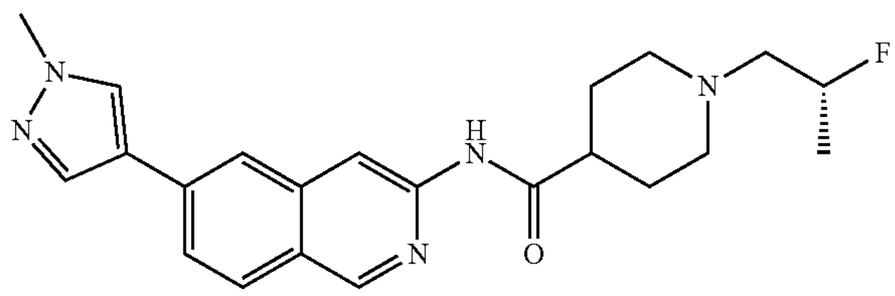
312



2-Fluoro-2-methyl-N-(6-(1-methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl) propanamide 312

Off-white solid (21.0 mg, 0.067 mmol, 10.5% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.64 (d, J=22.00 Hz, 6H), 4.15 (s, 3H), 8.07 (dd, J=8.51, 1.65 Hz, 1H), 8.16 (d, J=8.51 Hz, 1H), 8.36 (s, 1H), 8.46 (s, 1H), 8.74 (s, 1H), 9.17 (s, 1H), 9.91 (d, J=3.57 Hz, 1H); ESIMS found for $C_{16}H_{16}FN_5O$ m/z 314.1 (M+1).

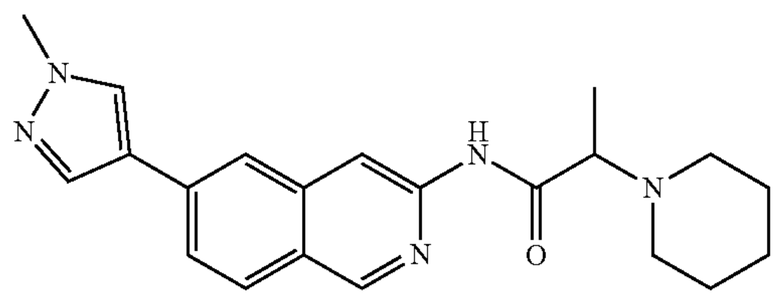
313



(R)-1-(2-Fluoropropyl)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl) piperidine-4-carboxamide 313

White solid (30.0 mg, 0.076 mmol, 25.4% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.26 (dd, J=23.90, 6.30 Hz, 3H), 1.68 (q, J=11.53 Hz, 2H), 1.74-1.81 (m, 2H), 1.99-2.09 (m, 2H), 2.35-2.47 (m, 1H), 2.52-2.57 (m, 1H), 2.93 (br t, J=11.80 Hz, 2H), 3.90 (s, 3H), 4.74-4.94 (m, 1H), 7.74 (dd, J=8.51, 1.37 Hz, 1H), 8.00 (d, J=8.51 Hz, 1H), 8.03 (s, 1H), 8.07 (s, 1H), 8.35 (s, 1H), 8.44 (s, 1H), 9.02 (s, 1H), 10.46 (s, 1H); ESIMS found for $C_{22}H_{26}FN_5O$ m/z 396.2 (M+1).

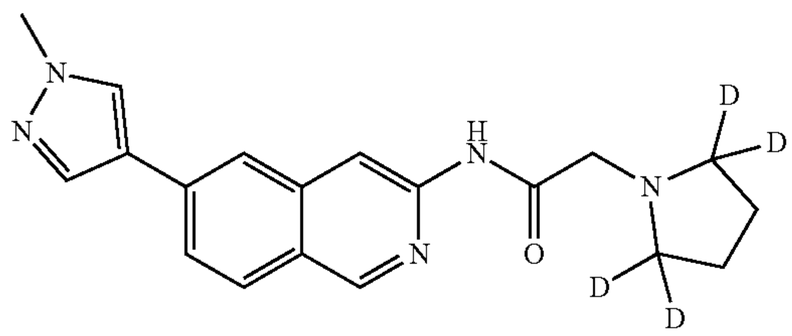
314



N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(piperidin-1-yl) propanamide 314

Off-white solid (57.0 mg, 0.157 mmol, 51.6% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.20 (d, J=7.14 Hz, 3H), 1.39-1.46 (m, 2H), 1.53-1.64 (m, 4H), 2.52-2.58 (m, 2H), 3.44 (q, J=6.86 Hz, 1H), 3.90 (s, 3H), 7.76 (dd, J=8.51, 1.65 Hz, 1H), 8.02 (d, J=8.51 Hz, 1H), 8.06-8.11 (m, 2H), 8.36 (s, 1H), 8.44 (s, 1H), 9.04 (s, 1H), 10.09 (s, 1H); ESIMS found for $C_{21}H_{25}N_5O$ m/z 364.2 (M+1).

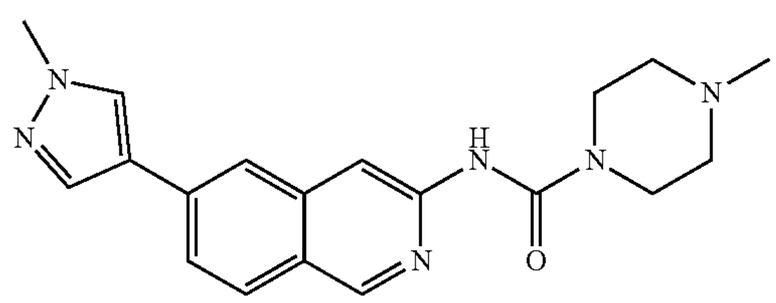
315



N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(pyrrolidin-1-yl-2,2,5,5-d_4)acetamide 315

Beige solid (43.0 mg, 0.127 mmol, 42.8% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.76 (s, 4H), 3.36 (s, 2H), 3.90 (s, 3H), 7.77 (dd, J=8.64, 1.51 Hz, 1H), 8.02 (d, J=8.51 Hz, 1H), 8.10 (s, 2H), 8.37 (s, 1H), 8.43 (s, 1H), 9.03 (s, 1H), 9.93 (s, 1H); ESIMS found for $C_{19}H_{17}D_4N_5O$ m/z 340.2 (M+1).

316

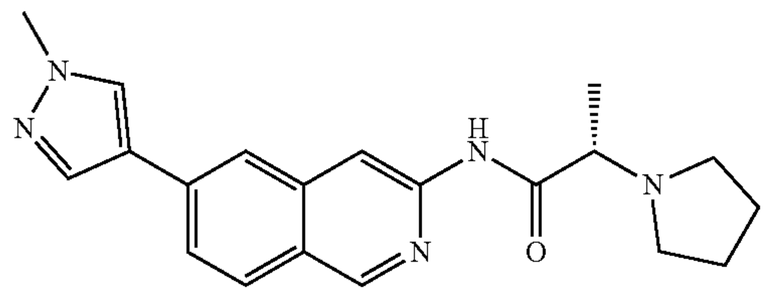


4-Methyl-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)piperazine-1-carboxamide 316

Off-white solid (14.0 mg, 0.040 mmol, 46.5% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 2.20 (s, 3H), 2.29-2.35 (m, 4H), 3.48-3.54 (m, 4H), 3.90 (s, 3H), 7.68 (dd, J=8.51, 1.65 Hz, 1H), 7.94-8.00 (m, 2H), 8.06 (s, 1H), 8.14 (s, 1H),

8.33 (s, 1H), 8.97 (s, 1H), 9.13 (s, 1H); ESIMS found for $C_{19}H_{22}N_6O$ m/z 351.2 (M+1).

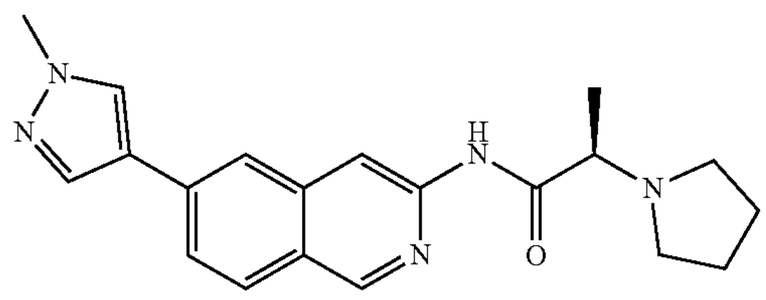
317



(S)—N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(pyrrolidin-1-yl) propanamide 317

White solid (75.0 mg, 0.215 mmol, 65.4% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.30 (3H, d, J=6.86 Hz), 1.74 (4H, br s), 2.57-2.68 (4H, m), 3.25-3.30 (1H, m), 3.90 (3H, s), 7.76 (1H, dd, J=8.51, 1.65 Hz), 8.02 (1H, d, J=8.51 Hz), 8.08 (1H, s), 8.09 (1H, s), 8.36 (1H, s), 8.43 (1H, s), 9.03 (1H, s), 9.94 (1H, s); ESIMS found for $C_{20}H_{23}N_5O$ m/z 350.2 (M+1).

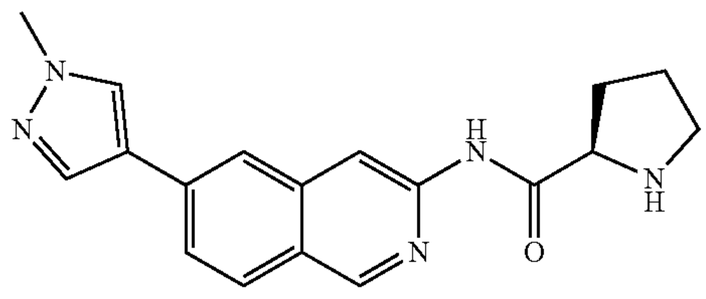
318



(R)—N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(pyrrolidin-1-yl) propanamide 318

Light beige solid (89.0 mg, 0.255 mmol, 62.1% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.30 (3H, d, J=6.86 Hz), 1.74 (4H, br s), 2.56-2.70 (4H, m), 3.25-3.30 (1H, m), 3.90 (3H, s), 7.76 (1H, dd, J=8.51, 1.65 Hz), 8.02 (1H, d, J=8.51 Hz), 8.08 (1H, s), 8.09 (1H, s), 8.36 (1H, s), 8.43 (1H, s), 9.03 (1H, s), 9.94 (1H, s); ESIMS found for $C_{20}H_{23}N_5O$ m/z 350.2 (M+1).

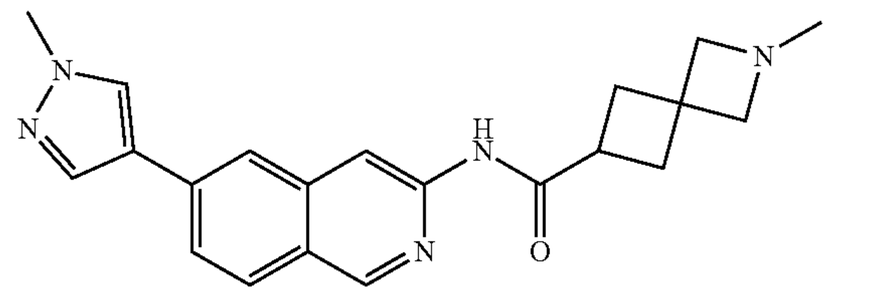
320



(R)—N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)pyrrolidine-2-carboxamide 320

Brown solid (830.0 mg, 2.58 mmol, 78.2% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.67 (2H, quin, J=6.86 Hz), 1.79-1.90 (1H, m), 2.04-2.16 (1H, m), 2.87 (1H, dt, J=10.15, 6.31 Hz), 2.97 (1H, dt, J=10.15, 6.72 Hz), 3.35 (1H, br s), 3.80 (1H, dd, J=9.19, 5.35 Hz), 3.90 (3H, s), 7.76 (1H, dd, J=8.51, 1.65 Hz), 8.02 (1H, d, J=8.51 Hz), 8.09 (1H, br s), 8.09 (1H, s), 8.36 (1H, s), 8.44 (1H, s), 9.02 (1H, s), 10.34 (1H, s); ESIMS found for $C_{18}H_{19}N_5O$ m/z 322.15 (M+1).

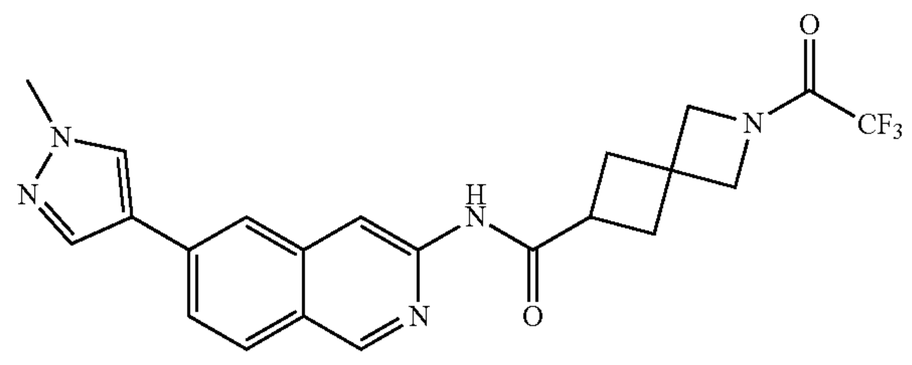
324



2-Methyl-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-azaspiro[3.3] heptane-6-carboxamide 324

Off-white solid (32.0 mg, 0.089 mmol, 38.4% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 2.15 (3H, s), 2.21-2.35 (4H, m), 3.04 (2H, s), 3.14 (2H, s), 3.21-3.28 (1H, m), 3.90 (3H, s), 7.74 (1H, dd, J=8.51, 1.65 Hz), 7.99 (1H, d, J=8.51 Hz), 8.04 (1H, s), 8.08 (1H, s), 8.35 (1H, s), 8.44 (1H, s), 9.01 (1H, s), 10.35 (1H, s); ESIMS found for $C_{21}H_{23}N_5O$ m/z 362.2 (M+1).

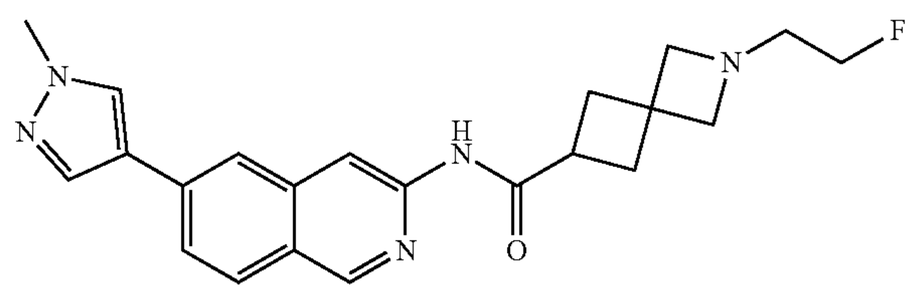
325



N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(2,2,2-trifluoroacetyl)-2-azaspiro[3.3]heptane-6-carboxamide 325

White solid (26.0 mg, 0.059 mmol, 18.0% yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 2.40-2.49 (4H, m), 3.22-3.31 (1H, m), 4.06-4.15 (2H, m), 4.44 (2H, br d, J=17.56 Hz), 7.75 (1H, dd, J=8.51, 1.65 Hz), 8.00 (1H, d, J=8.51 Hz), 8.06 (1H, s), 8.09 (1H, d, J=1.10 Hz), 8.35 (1H, d, J=1.65 Hz), 8.46 (1H, s), 9.02 (1H, s), 10.47 (1H, s); ESIMS found for $C_{22}H_{20}F_3N_5O_2$ m/z 444.15 (M+1).

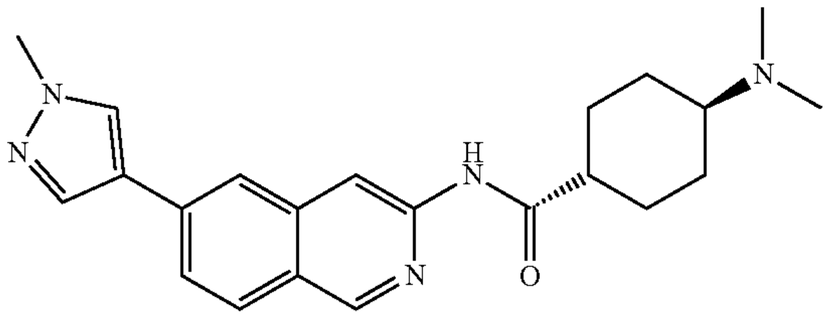
326



2-(2-Fluoroethyl)-N-(6-(1-methyl-1H-pyrazol-4-yl) isoquinolin-3-yl)-2-azaspiro[3.3]heptane-6-carboxamide 326

Beige solid (10.0 mg, 0.025 mmol, 24.9% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 2.23-2.36 (4H, m), 2.60 (2H, dt, J=29.00, 5.00 Hz), 3.13 (2H, s), 3.22 (2H, s), 3.24-3.29 (1H, m), 4.36 (2H, dt, J=48.00, 5.00 Hz), 7.74 (1H, dd, J=8.51, 1.37 Hz), 7.99 (1H, d, J=8.51 Hz), 8.04 (1H, s), 8.08 (1H, s), 8.35 (1H, s), 8.44 (1H, s), 9.01 (1H, s), 10.36 (1H, s); ESIMS found for $C_{22}H_{24}FN_5O$ m/z 394.2 (M+1).

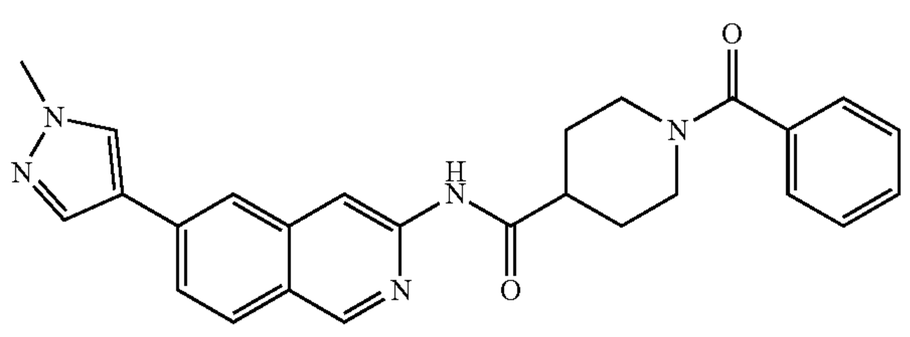
327



trans-4-(Dimethylamino)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)cyclohexane-1-carboxamide 327

Beige solid (650.0 mg, 1.72 mmol, 46.3% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.11-1.27 (3H, m), 1.41-1.54 (2H, m), 1.83-1.96 (4H, m), 2.10-2.16 (1H, m), 2.18 (6H, s), 2.42-2.49 (1H, m), 3.90 (3H, s), 7.74 (1H, dd, J=8.51, 1.37 Hz), 7.99 (1H, d, J=8.51 Hz), 8.02 (1H, s), 8.07 (1H, s), 8.35 (1H, s), 8.43 (1H, s), 9.02 (1H, s), 10.41 (1H, s); ESIMS found for $C_{22}H_{27}N_5O$ m/z 378.2 (M+1).

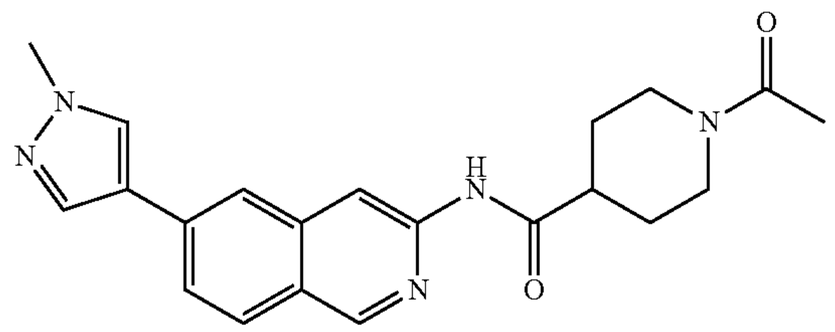
328



1-Benzoyl-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)piperidine-4-carboxamide 328

White solid (65.0 mg, 0.148 mmol, 55.3% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.57-1.72 (2H, m), 1.75-2.00 (2H, m), 2.86 (2H, tt, J=11.18, 3.77 Hz), 3.04-3.19 (1H, m), 3.57-3.75 (1H, m), 3.90 (3H, s), 4.43-4.63 (1H, m), 7.38-7.43 (2H, m), 7.43-7.49 (3H, m), 7.75 (1H, dd, J=8.51, 1.37 Hz), 8.00 (1H, d, J=8.51 Hz), 8.04 (1H, s), 8.08 (1H, s), 8.35 (1H, s), 8.43 (1H, s), 9.03 (1H, s), 10.54 (1H, s); ESIMS found for $C_{26}H_{25}N_5O_2$ m/z 440.0 (M+1).

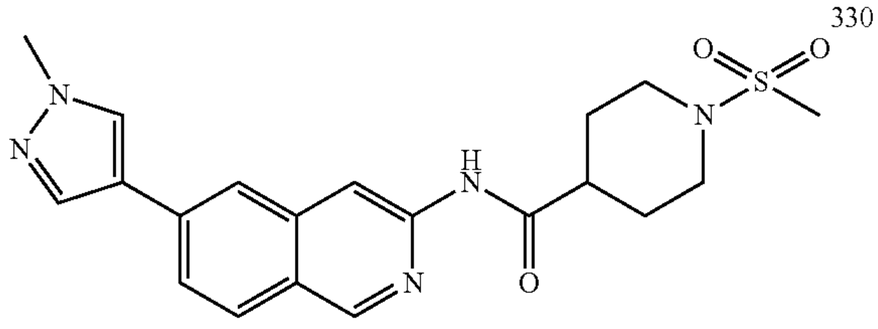
329



1-Acetyl-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)piperidine-4-carboxamide 329

White solid (60.0 mg, 0.159 mmol, 59.4% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.47 (1H, qd, J=12.26, 4.39 Hz), 1.56-1.69 (1H, m), 1.77-1.91 (2H, m), 2.02 (3H, s), 2.58 (1H, td, J=12.62, 2.47 Hz), 2.75-2.84 (1H, m), 3.03-3.11 (1H, m), 3.88 (1H, br d, J=13.15 Hz), 3.90 (3H, s), 4.41 (1H, br d, J=13.17 Hz), 7.75 (1H, dd, J=8.51, 1.65 Hz), 8.00 (1H, d, J=8.51 Hz), 8.04 (1H, s), 8.08 (1H, s), 8.35 (1H, s), 8.43 (1H, s), 9.03 (1H, s), 10.53 (1H, s); ESIMS found for $C_{21}H_{23}N_5O_2$ m/z 378.0 (M+1).

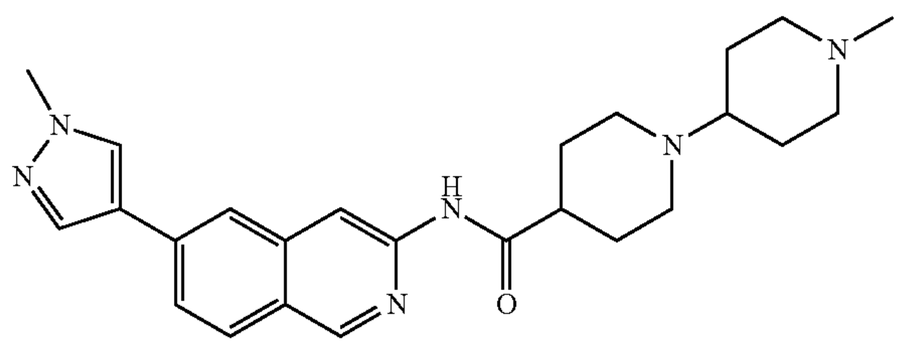
330



N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-1-(methylsulfonyl) piperidine-4-carboxamide 330

White solid (60.0 mg, 0.145 mmol, 54.2% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.65-1.77 (2H, m), 1.95 (2H, br dd, J=13.31, 2.61 Hz), 2.69 (1H, tt, J=11.25, 3.84 Hz), 2.76 (2H, td, J=11.94, 2.20 Hz), 2.89 (3H, s), 3.59-3.67 (2H, m), 3.90 (3H, s), 7.75 (1H, dd, J=8.51, 1.65 Hz), 8.01 (1H, d, J=8.51 Hz), 8.05 (1H, s), 8.08 (1H, s), 8.35 (1H, s), 8.44 (1H, s), 9.03 (1H, s), 10.59 (1H, s); ESIMS found for $C_{20}H_{23}N_5O_3S$ m/z 413.9 (M+1).

331

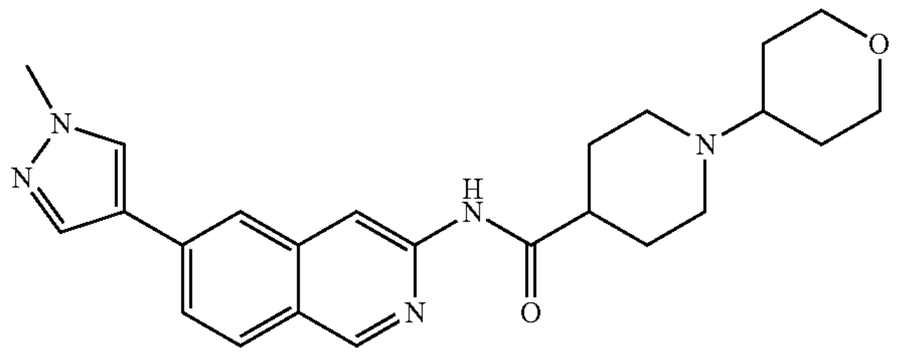


1'-Methyl-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-[1,4'-bipiperidine]-4-carboxamide 331

White solid (4.0 mg, 0.009 mmol, 3.1% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.44 (2H, qd, J=11.89, 3.57

Hz), 1.58-1.71 (4H, m), 1.73-1.87 (4H, m), 2.06-2.20 (4H, m), 2.12 (3H, s), 2.78 (2H, br d, J=11.53 Hz), 2.91 (2H, br d, J=11.25 Hz), 3.90 (3H, s), 7.74 (1H, dd, J=8.51, 1.37 Hz), 7.99 (1H, d, J=8.78 Hz), 8.03 (1H, s), 8.07 (1H, s), 8.34 (1H, s), 8.44 (1H, s), 9.02 (1H, s), 10.42 (1H, s); ESIMS found for $C_{25}H_{32}N_6O$ m/z 433.0 (M+1).

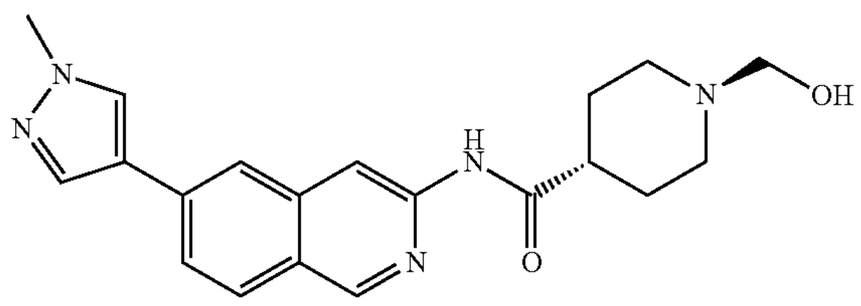
332



N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-1-(tetrahydro-2H-pyran-4-yl)piperidine-4-carboxamide 332

White solid (11.0 mg, 0.026 mmol, 8.8% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.43 (2H, qd, J=12.08, 4.39 Hz), 1.59-1.69 (4H, m), 1.79 (2H, br d, J=11.80 Hz), 2.08-2.17 (2H, m), 2.42 (1H, tt, J=11.35, 3.60 Hz), 2.51-2.58 (1H, m), 2.94 (2H, br d, J=11.53 Hz), 3.22-3.29 (2H, m), 3.87 (2H, br d, J=3.57 Hz), 3.90 (3H, s), 7.74 (1H, dd, J=8.51, 1.65 Hz), 7.99 (1H, d, J=8.78 Hz), 8.03 (1H, s), 8.07 (1H, s), 8.34 (1H, s), 8.44 (1H, s), 9.02 (1H, s), 10.43 (1H, s); ESIMS found for $C_{24}H_{29}N_5O_2$ m/z 420.0 (M+1).

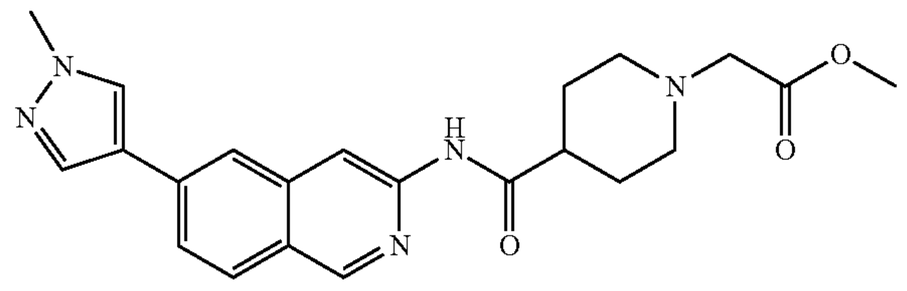
333



trans-4-(Hydroxymethyl)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)cyclohexane-1-carboxamide 333

Light beige solid (215.0 mg, 0.59 mmol, 51.3% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 0.95 (2H, qd, J=12.72, 3.29 Hz), 1.31-1.39 (1H, m), 1.45 (2H, qd, J=12.72, 3.02 Hz), 1.80 (2H, br dd, J=13.17, 2.74 Hz), 1.84-1.93 (2H, m), 3.24 (2H, t, J=5.76 Hz), 3.90 (3H, s), 4.37 (1H, t, J=5.35 Hz), 7.74 (1H, dd, J=8.51, 1.65 Hz), 7.99 (1H, d, J=8.51 Hz), 8.02 (1H, s), 8.07 (1H, s), 8.34 (1H, s), 8.43 (1H, s), 9.02 (1H, s), 10.38 (1H, s); ESIMS found for $C_{21}H_{24}N_4O_2$ m/z 365.0 (M+1).

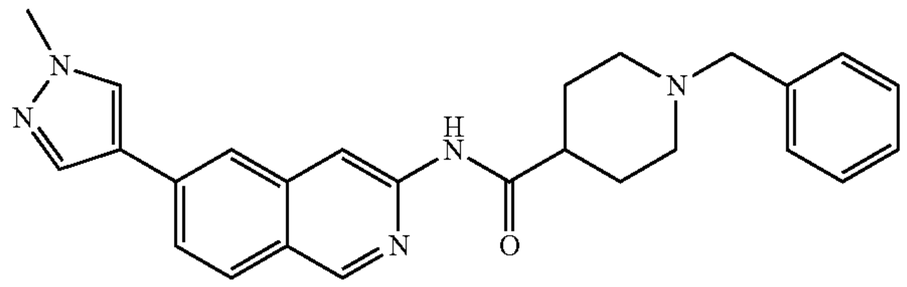
334



Methyl 2-(4-((6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)carbamoyl) piperidin-1-yl)acetate 334

White solid (20.0 mg, 0.049 mmol, 16.5% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.62-1.73 (2H, m), 1.74-1.82 (2H, m), 2.22 (2H, td, J=11.53, 2.20 Hz), 2.51-2.58 (1H, m), 2.84-2.92 (2H, m), 3.24 (2H, s), 3.62 (3H, s), 3.90 (3H, s), 7.74 (1H, dd, J=8.51, 1.65 Hz), 8.00 (1H, d, J=8.51 Hz), 8.03 (1H, s), 8.07 (1H, s), 8.34 (1H, s), 8.44 (1H, s), 9.02 (1H, s), 10.45 (1H, s); ESIMS found for $C_{22}H_{25}N_5O_3$ m/z 408.0 (M+1).

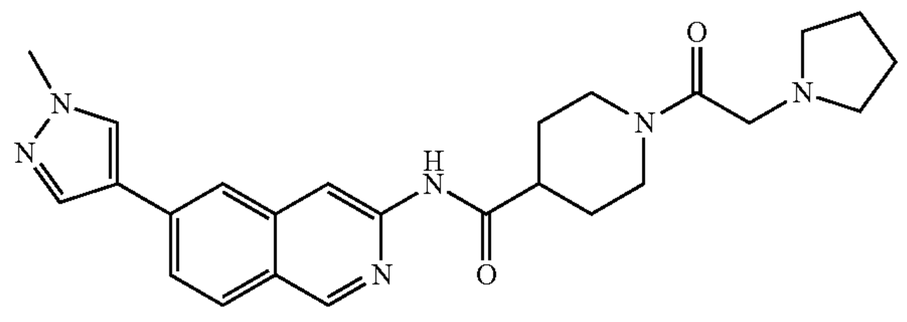
335



1-Benzyl-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)piperidine-4-carboxamide 335

White solid (22.0 mg, 0.052 mmol, 17.3% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.60-1.72 (2H, m), 1.73-1.81 (2H, m), 1.98 (2H, td, J=11.60, 2.06 Hz), 2.51-2.57 (1H, m), 2.88-2.96 (2H, m), 3.24 (2H, s), 3.90 (3H, s), 7.74 (1H, dd, J=8.51, 1.65 Hz), 7.99 (1H, d, J=8.78 Hz), 8.03 (1H, s), 8.07 (1H, s), 8.34 (1H, s), 8.44 (1H, s), 9.02 (1H, s), 10.43 (1H, s); ESIMS found for $C_{26}H_{27}N_5O$ m/z 426.0 (M+1).

336

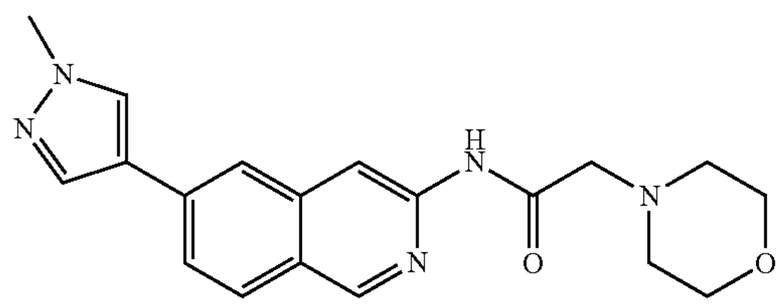


N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-1-(2-(pyrrolidin-1-yl) acetyl)piperidine-4-carboxamide 336

White solid (21.0 mg, 0.047 mmol, 15.8% yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.43-1.54 (1H, m), 1.55-1.66 (1H, m), 1.67-1.73 (4H, m), 1.84 (2H, br d,

J=10.98 Hz), 2.48 (4H, br s), 2.56-2.66 (1H, m), 2.76-2.87 (1H, m), 2.97-3.07 (1H, m), 3.32 (2H, br s), 3.90 (3H, s), 4.11 (1H, br d, J=13.17 Hz), 4.40 (1H, br d, J=12.90 Hz), 7.75 (1H, dd, J=8.51, 1.65 Hz), 8.00 (1H, d, J=8.51 Hz), 8.04 (1H, s), 8.07 (1H, s), 8.34 (1H, s), 8.43 (1H, s), 9.03 (1H, s), 10.52 (1H, s); ESIMS found for $C_{25}H_{30}N_6O_2$ m/z 447.0 (M+1).

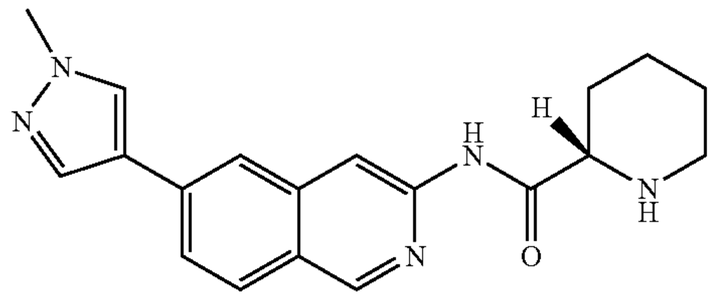
338



N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-morpholinoacetamide 338

Beige solid (13.0 mg, 0.037 mmol, 33.6% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 2.55-2.60 (3H, m), 3.24 (2H, s), 3.62-3.70 (4H, m), 3.90 (3H, s), 7.77 (1H, dd, J=8.51, 1.65 Hz), 8.02 (1H, d, J=8.51 Hz), 8.09 (2H, s), 8.35 (1H, s), 8.43 (1H, s), 9.04 (1H, s), 9.97 (1H, s); ESIMS found for $C_{19}H_{21}N_5O_2$ m/z 352.0 (M+1).

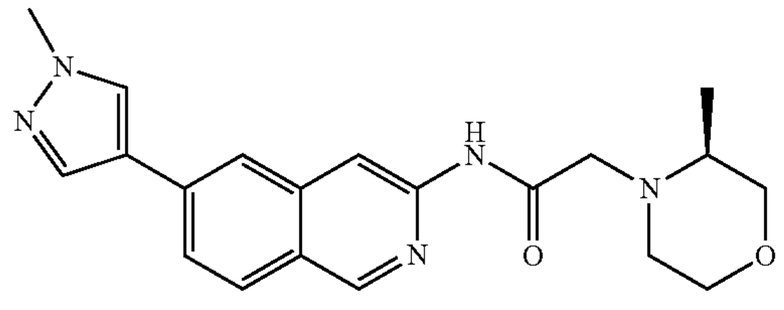
340



(S)—N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)piperidine-2-carboxamide 340

Light beige solid (35.0 mg, 0.104 mmol, 56.8% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.31-1.41 (1H, m), 1.41-1.47 (2H, m), 1.47-1.56 (1H, m), 1.72-1.79 (1H, m), 1.84-1.91 (1H, m), 2.58-2.64 (1H, m), 2.93-3.00 (1H, m), 3.34 (1H, br dd, J=9.19, 3.16 Hz), 3.90 (3H, s), 7.76 (1H, dd, J=8.51, 1.65 Hz), 8.01 (1H, d, J=8.51 Hz), 8.07 (1H, br s), 8.08 (1H, s), 8.35 (1H, s), 8.43 (1H, s), 9.03 (1H, s), 9.85 (1H, br s); ESIMS found for $C_{19}H_{21}N_5O$ m/z 336.0 (M+1).

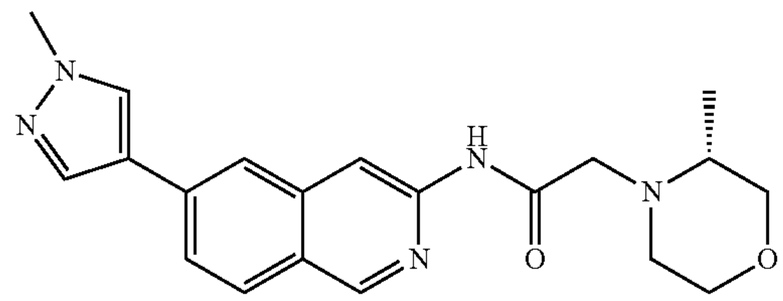
341



(S)—N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(3-methylmorpholino)acetamide 341

Beige solid (32.5 mg, 0.089 mmol, 34.2% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 0.95 (3H, d, J=6.59 Hz), 2.52-2.58 (1H, m), 2.58-2.65 (1H, m), 2.81 (1H, dt, J=11.80, 2.47 Hz), 3.15-3.23 (2H, m), 3.47 (1H, d, J=16.47 Hz), 3.58 (1H, td, J=10.70, 2.20 Hz), 3.68 (1H, dd, J=11.25, 2.74 Hz), 3.71-3.79 (1H, m), 3.90 (3H, s), 7.77 (1H, dd, J=8.51, 1.37 Hz), 8.03 (1H, d, J=8.51 Hz), 8.10 (1H, s), 8.11 (1H, br s), 8.37 (1H, s), 8.44 (1H, s), 9.04 (1H, s), 9.97 (1H, s); ESIMS found for $C_{20}H_{23}N_5O_2$ m/z 366.2 (M+1).

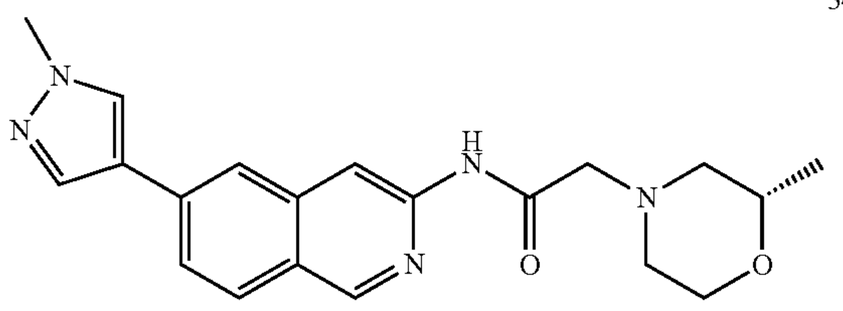
342



(R)—N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(3-methylmorpholino)acetamide 342

Beige solid (37.0 mg, 0.101 mmol, 38.9% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 0.96 (3H, d, J=6.59 Hz), 2.55 (1H, ddd, J=11.80, 10.15, 3.02 Hz), 2.61 (1H, ddd, J=9.13, 6.24, 3.02 Hz), 2.81 (1H, dt, J=11.73, 2.50 Hz), 3.13-3.23 (2H, m), 3.47 (1H, d, J=16.47 Hz), 3.58 (1H, td, J=10.70, 2.20 Hz), 3.68 (1H, dd, J=11.25, 3.02 Hz), 3.74 (1H, dt, J=11.32, 2.71 Hz), 3.90 (3H, s), 7.77 (1H, dd, J=8.64, 1.51 Hz), 8.02 (1H, d, J=8.51 Hz), 8.10 (1H, s), 8.10 (1H, br s), 8.36 (1H, s), 8.43 (1H, s), 9.04 (1H, s), 9.97 (1H, s); ESIMS found for $C_{20}H_{23}N_5O_2$ m/z 366.2 (M+1).

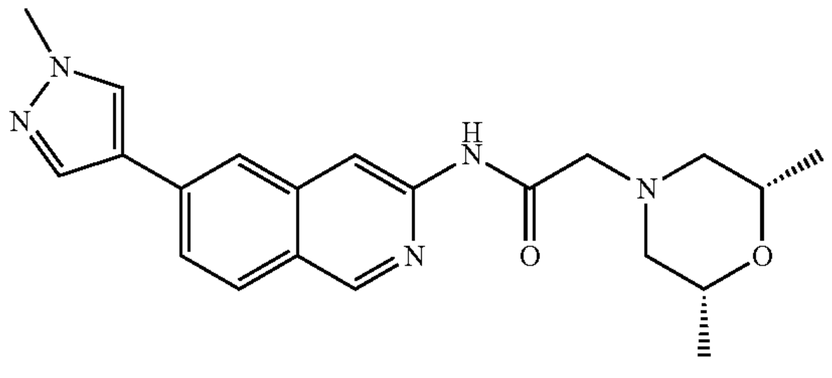
343



(S)—N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(2-methylmorpholino)acetamide 343

Beige solid (19.0 mg, 0.052 mmol, 15.8% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.07 (3H, d, J=6.31 Hz), 2.00 (1H, dd, J=10.98, 10.15 Hz), 2.30 (1H, td, J=11.39, 3.02 Hz), 2.73-2.79 (1H, m), 2.83 (1H, br d, J=11.25 Hz), 3.23 (2H, d, J=1.92 Hz), 3.53-3.66 (2H, m), 3.75-3.81 (1H, m), 3.90 (3H, s), 7.77 (1H, dd, J=8.64, 1.51 Hz), 8.02 (1H, d, J=8.78 Hz), 8.10 (2H, s), 8.37 (1H, s), 8.44 (1H, s), 9.04 (1H, s), 10.00 (1H, s); ESIMS found for $C_{20}H_{23}N_5O_2$ m/z 366.2 (M+1).

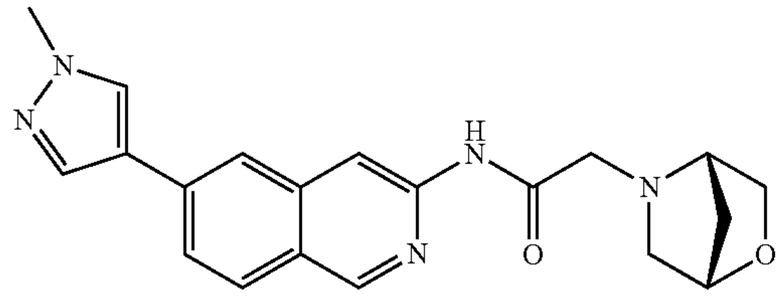
344



2-((2R,6S)-2,6-Dimethylmorpholino)-N-(6-(1-methyl-1H-pyrazol-4-yl) isoquinolin-3-yl)acetamide 344

Off-white solid (53.0 mg, 0.140 mmol, 46.6% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.07 (6H, d, J=6.31 Hz), 1.92 (2H, t, J=10.84 Hz), 2.82 (2H, br d, J=10.15 Hz), 3.22 (2H, s), 3.62-3.71 (2H, m), 3.90 (3H, s), 7.77 (1H, dd, J=8.51, 1.65 Hz), 8.02 (1H, d, J=8.51 Hz), 8.10 (2H, s), 8.36 (1H, s), 8.44 (1H, s), 9.04 (1H, s), 9.98 (1H, s); ESIMS found for $C_{21}H_{25}N_5O_2$ m/z 380.2 (M+1).

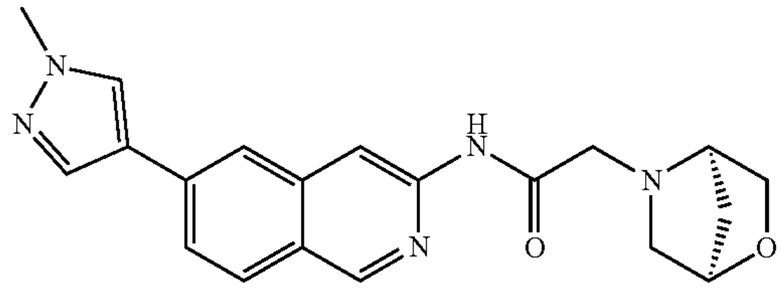
345



2-((1S,4S)-2-Oxa-5-azabicyclo[2.2.1]heptan-5-yl)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl) acetamide 345

Ash colored solid (22.0 mg, 0.061 mmol, 18.3% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.67 (1H, dt, J=9.61, 1.10 Hz), 1.87 (1H, dd, J=9.74, 1.78 Hz), 2.62 (1H, d, J=10.43 Hz), 2.95 (1H, dd, J=10.02, 1.51 Hz), 3.45 (2H, d, J=5.21 Hz), 3.59 (1H, dd, J=7.82, 1.78 Hz), 3.63 (1H, s), 3.88 (1H, d, J=7.68 Hz), 3.90 (3H, s), 4.41 (1H, s), 7.77 (1H, dd, J=8.64, 1.51 Hz), 8.03 (1H, d, J=8.78 Hz), 8.10 (1H, s), 8.11 (1H, br s), 8.37 (1H, s), 8.44 (1H, s), 9.04 (1H, s), 9.92 (1H, s); ESIMS found for $C_{20}H_{21}N_5O_2$ m/z 364.2 (M+1).

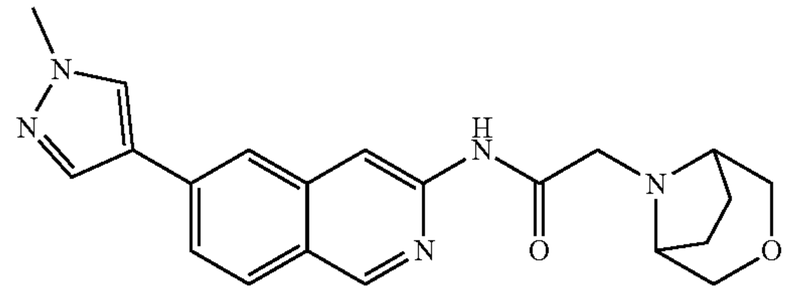
346



2-((1R,4R)-2-Oxa-5-azabicyclo[2.2.1]heptan-5-yl)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl) acetamide 346

Ash colored solid (25.0 mg, 0.069 mmol, 18.3% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.63-1.70 (1H, m), 1.87 (1H, dd, J=9.74, 1.78 Hz), 2.62 (1H, d, J=10.15 Hz), 2.95 (1H, dd, J=10.02, 1.51 Hz), 3.45 (2H, d, J=4.94 Hz), 3.59 (1H, dd, J=7.68, 1.92 Hz), 3.63 (1H, s), 3.88 (1H, d, J=7.68 Hz), 3.90 (3H, s), 4.41 (1H, s), 7.77 (1H, dd, J=8.51, 1.65 Hz), 8.03 (1H, d, J=8.51 Hz), 8.10 (1H, s), 8.11 (1H, br s), 8.37 (1H, s), 8.44 (1H, s), 9.04 (1H, s), 9.92 (1H, s); ESIMS found for $C_{20}H_{21}N_5O_2$ m/z 364.2 (M+1).

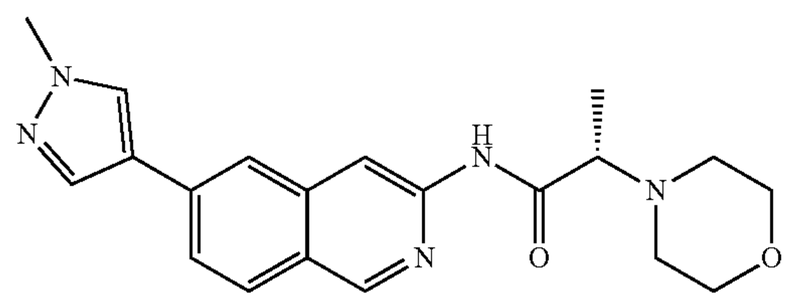
347



2-(3-Oxa-8-azabicyclo[3.2.1]octan-8-yl)-N-(6-(1-methyl-1H-pyrazol-4-yl) isoquinolin-3-yl)acetamide 347

Off-white solid (8.0 mg, 0.021 mmol, 8.2% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.75-1.82 (2H, m), 1.86-1.94 (2H, m), 3.14 (2H, s), 3.17 (2H, br d, J=0.82 Hz), 3.48-3.55 (2H, m), 3.68 (2H, d, J=10.43 Hz), 3.90 (3H, s), 7.78 (1H, dd, J=8.51, 1.37 Hz), 8.03 (1H, d, J=8.51 Hz), 8.10 (1H, s), 8.11 (1H, s), 8.37 (1H, s), 8.46 (1H, s), 9.06 (1H, s), 10.15 (1H, s); ESIMS found for $C_{21}H_{23}N_5O_2$ m/z 378.2 (M+1).

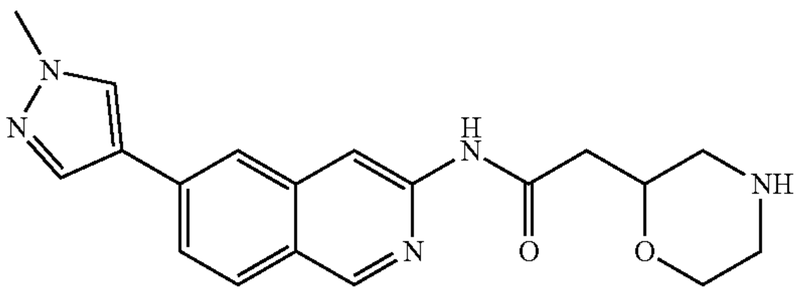
348



(S)—N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-morpholinopropanamide 348

Light yellow solid (68.0 mg, 0.186 mmol, 45.3% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.23 (3H, d, J=6.86 Hz), 2.51-2.57 (2H, m), 2.57-2.65 (2H, m), 3.45 (1H, q, J=6.77 Hz), 3.64 (4H, t, J=4.67 Hz), 3.90 (3H, s), 7.77 (1H, dd, J=8.51, 1.37 Hz), 8.02 (1H, d, J=8.51 Hz), 8.08 (1H, s), 8.09 (1H, s), 8.36 (1H, s), 8.45 (1H, s), 9.04 (1H, s), 10.17 (1H, s); ESIMS found for $C_{20}H_{23}N_5O_2$ m/z 366.2 (M+1).

349

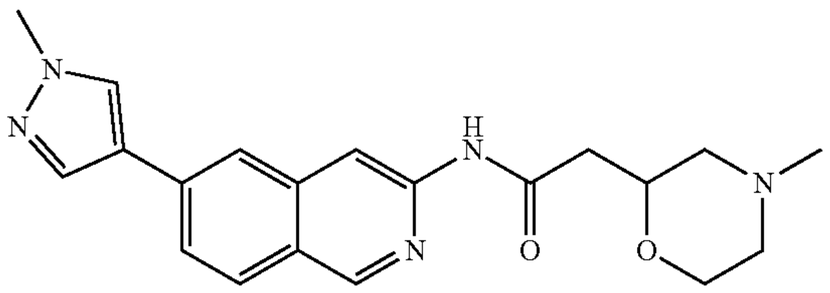


N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(morpholin-2-yl) acetamide 349

Off-white solid (275.0 mg, 0.783 mmol, 91.8% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 2.41-2.48 (2H, m), 2.57-2.69 (3H, m), 2.83 (1H, br dd, J=12.21, 2.06 Hz), 3.43 (1H, td, J=10.63, 3.43 Hz), 3.70 (1H, br d, J=10.70 Hz), 3.78-3.85 (1H, m), 3.90 (3H, s), 7.74 (1H, dd, J=8.64, 1.51

Hz), 8.00 (1H, d, J=8.51 Hz), 8.04 (1H, s), 8.07 (1H, s), 8.34 (1H, s), 8.43 (1H, s), 9.02 (1H, s), 10.41 (1H, s); ESIMS found for $C_{19}H_{21}N_5O_2$ m/z 352.0 (M+1).

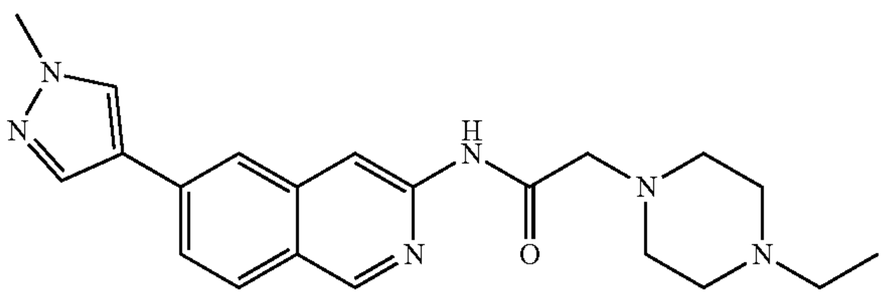
350



N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(4-methylmorpholin-2-yl)acetamide 350

White solid (71.0 mg, 0.194 mmol, 68.3% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.78 (1H, t, J=11.00 Hz), 1.97 (1H, td, J=11.32, 3.16 Hz), 2.18 (3H, s), 2.53 (1H, br d, J=5.49 Hz), 2.58 (1H, br dd, J=11.25, 1.37 Hz), 2.66 (1H, dd, J=14.68, 7.82 Hz), 2.74 (1H, br d, J=11.25 Hz), 3.50 (1H, td, J=11.11, 2.47 Hz), 3.72-3.80 (1H, m), 3.86-3.96 (1H, m), 3.90 (3H, s), 7.75 (1H, dd, J=8.51, 1.65 Hz), 8.00 (1H, d, J=8.51 Hz), 8.04 (1H, s), 8.07 (1H, s), 8.34 (1H, s), 8.44 (1H, s), 9.02 (1H, s), 10.45 (1H, s); ESIMS found for $C_{20}H_{23}N_5O_2$ m/z 366.0 (M+1).

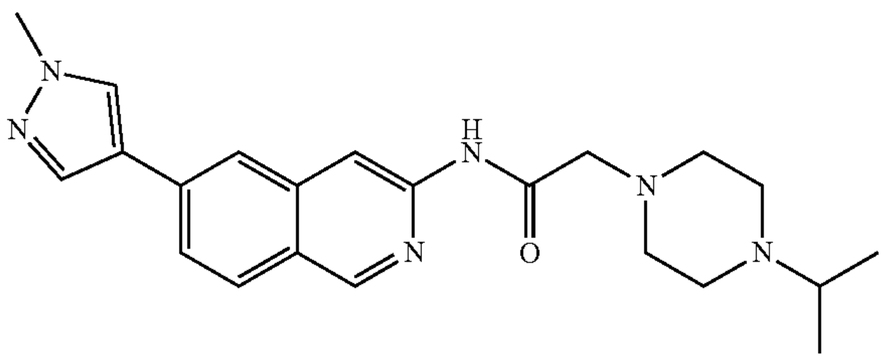
351



2-(4-Ethylpiperazin-1-yl)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl) acetamide 351

Beige solid (52.0 mg, 0.137 mmol, 52.8% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.03 (3H, br s), 2.30-2.47 (4H, m), 2.53-2.74 (6H, m), 3.24 (2H, br s), 3.90 (3H, s), 7.77 (1H, dd, J=8.51, 1.37 Hz), 8.02 (1H, d, J=8.51 Hz), 8.10 (2H, s), 8.37 (1H, s), 8.43 (1H, s), 9.04 (1H, s), 9.96 (1H, br s); ESIMS found for $C_{21}H_{26}N_6O$ m/z 379.2 (M+1).

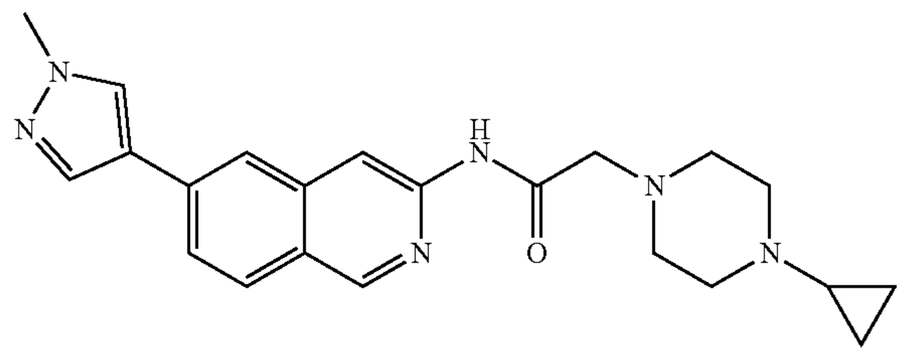
352



2-(4-Isopropylpiperazin-1-yl)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)acetamide 352

Beige solid (66.0 mg, 0.162 mmol, 66.7% yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 0.99 (6H, d, J=6.59 Hz), 2.51-2.54 (2H, m), 2.57 (4H, br s), 2.61-2.69 (1H, m), 3.20 (2H, s), 3.90 (3H, s), 7.77 (1H, dd, J=8.64, 1.51 Hz), 8.02 (1H, d, J=8.51 Hz), 8.10 (2H, s), 8.36 (1H, s), 8.43 (1H, s), 9.04 (1H, s), 9.89 (1H, s); ESIMS found for $C_{22}H_{28}N_6O$ m/z 393.0 (M+1).

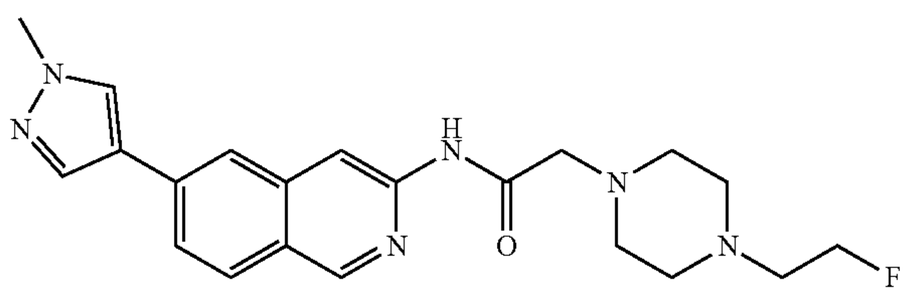
353



2-(4-Cyclopropylpiperazin-1-yl)-N-(6-(1-methyl-1H-pyrazol-4-yl) isoquinolin-3-yl)acetamide 353

Beige solid (44.0 mg, 0.109 mmol, 44.7% yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 0.26-0.32 (2H, m), 0.39-0.45 (2H, m), 1.66 (1H, tt, J=6.59, 3.43 Hz), 2.51-2.57 (4H, m), 2.62 (4H, br s), 3.20 (2H, s), 3.90 (3H, s), 7.77 (1H, dd, J=8.51, 1.65 Hz), 8.02 (1H, d, J=8.78 Hz), 8.09 (2H, s), 8.36 (1H, s), 8.43 (1H, s), 9.04 (1H, s), 9.92 (1H, s); ESIMS found for $C_{22}H_{26}N_6O$ m/z 391.0 (M+1).

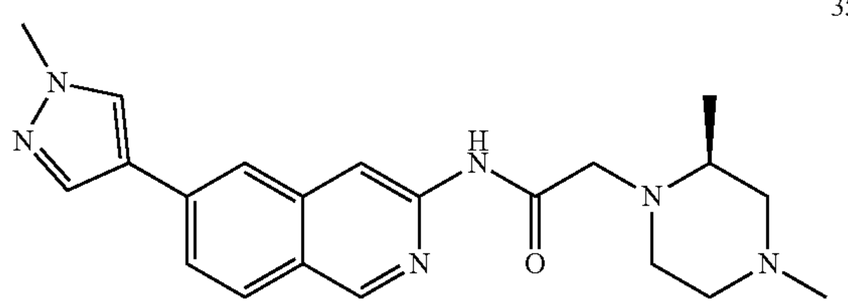
354



2-(4-(2-Fluoroethyl)piperazin-1-yl)-N-(6-(1-methyl-1H-pyrazol-4-yl) isoquinolin-3-yl)acetamide 354

Off-white solid (33.0 mg, 0.083 mmol, 25.9% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 2.54 (4H, br s), 2.57-2.60 (3H, m), 2.64 (4H, dt, J=28.60, 4.95 Hz), 3.22 (2H, s), 3.90 (3H, s), 4.54 (2H, dt, J=47.80, 4.70 Hz), 7.77 (1H, dd, J=8.51, 1.65 Hz), 8.02 (1H, d, J=8.51 Hz), 8.10 (2H, s), 8.37 (1H, s), 8.43 (1H, s), 9.04 (1H, s), 9.93 (1H, s); ESIMS found for $C_{21}H_{25}FN_6O$ m/z 397.2 (M+1).

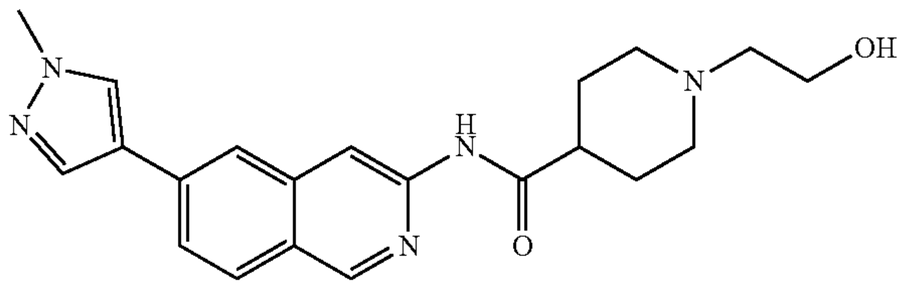
355



(S)-2-(2,4-Dimethylpiperazin-1-yl)-N-(6-(1-methyl-1H-pyrazol-4-yl) isoquinolin-3-yl)acetamide 355

Beige solid (20.0 mg, 0.053 mmol, 20.3% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.01 (3H, d, J=6.31 Hz), 1.87 (1H, br t, J=8.51 Hz), 2.11-2.19 (1H, m), 2.17 (3H, s), 2.51-2.57 (1H, m), 2.57-2.67 (3H, m), 2.83 (1H, dt, J=11.25, 3.02 Hz), 3.13 (1H, d, J=16.47 Hz), 3.43 (1H, d, J=16.74 Hz), 3.90 (3H, s), 7.77 (1H, dd, J=8.51, 1.65 Hz), 8.02 (1H, d, J=8.51 Hz), 8.10 (1H, s), 8.11 (1H, br s), 8.37 (1H, s), 8.43 (1H, s), 9.04 (1H, s), 9.92 (1H, s); ESIMS found for $C_{21}H_{26}N_6O$ m/z 379.2 (M+1).

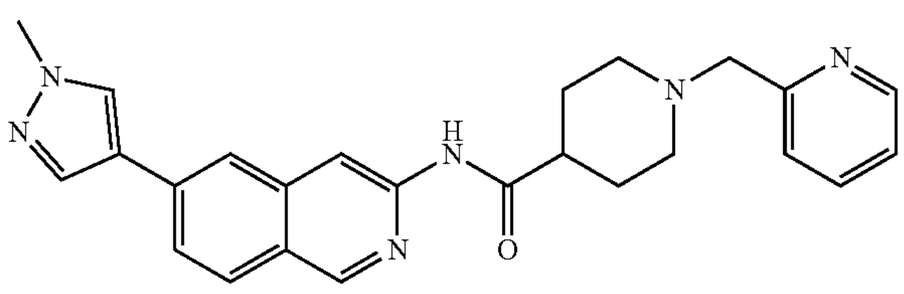
358



1-(2-Hydroxyethyl)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl) piperidine-4-carboxamide 358

White solid (41.0 mg, 0.108 mmol, 36.2% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.62-1.73 (2H, m), 1.73-1.81 (2H, m), 1.98 (2H, td, J=11.46, 2.06 Hz), 2.39 (2H, t, J=6.31 Hz), 2.52-2.57 (1H, m), 2.92 (2H, br d, J=11.53 Hz), 3.50 (2H, q, J=6.04 Hz), 3.90 (3H, s), 4.30 (1H, br t, J=5.35 Hz), 7.73 (1H, dd, J=8.51, 1.65 Hz), 7.99 (1H, d, J=8.51 Hz), 8.02 (1H, s), 8.06 (1H, s), 8.33 (1H, s), 8.44 (1H, s), 9.02 (1H, s), 10.39 (1H, s); ESIMS found for $C_{21}H_{25}N_5O_2$ m/z 380.0 (M+1).

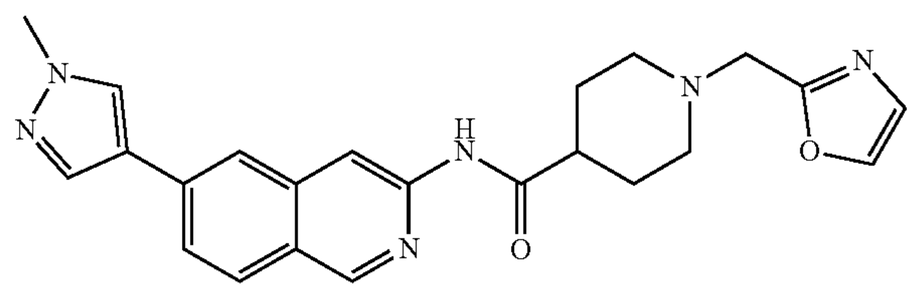
359



N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-1-(pyridin-2-ylmethyl) piperidine-4-carboxamide 359

Beige solid (11.0 mg, 0.026 mmol, 8.7% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.66-1.77 (2H, m), 1.77-1.84 (2H, m), 2.01-2.12 (2H, m), 2.53-2.62 (1H, m), 2.85-2.94 (2H, m), 3.60 (2H, s), 3.90 (3H, s), 7.25 (1H, dd, J=6.86, 5.49 Hz), 7.46 (1H, d, J=7.96 Hz), 7.74 (1H, dd, J=8.51, 1.65 Hz), 7.77 (1H, td, J=7.62, 1.78 Hz), 7.99 (1H, d, J=8.51 Hz), 8.03 (1H, s), 8.07 (1H, s), 8.33 (1H, s), 8.44 (1H, s), 8.49 (1H, br d, J=4.12 Hz), 9.02 (1H, s), 10.41 (1H, s); ESIMS found for $C_{25}H_{26}N_6O$ m/z 427.0 (M+1).

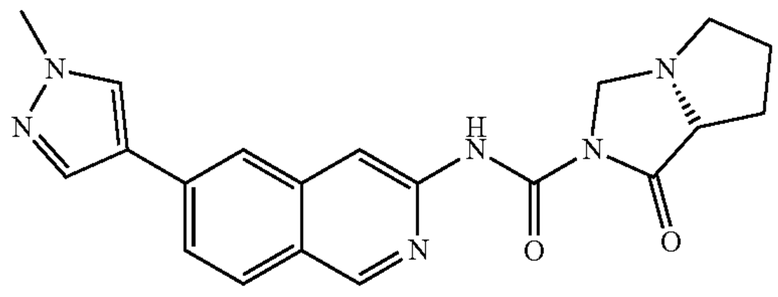
360



N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-1-(oxazol-2-ylmethyl) piperidine-4-carboxamide 360

White solid (65.0 mg, 0.156 mmol, 52.3% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.68 (2H, qd, J=12.21, 3.43 Hz), 1.79 (2H, br d, J=10.43 Hz), 2.07-2.18 (2H, m), 2.51-2.57 (1H, m), 2.85-2.94 (2H, m), 3.67 (2H, s), 3.90 (3H, s), 7.17 (1H, d, J=0.82 Hz), 7.73 (1H, dd, J=8.64, 1.51 Hz), 7.99 (1H, d, J=8.51 Hz), 8.02 (1H, s), 8.06 (1H, s), 8.06 (1H, d, J=0.82 Hz), 8.33 (1H, s), 8.43 (1H, s), 9.01 (1H, s), 10.40 (1H, s); ESIMS found for $C_{23}H_{24}N_6O_2$ m/z 416.95 (M+1).

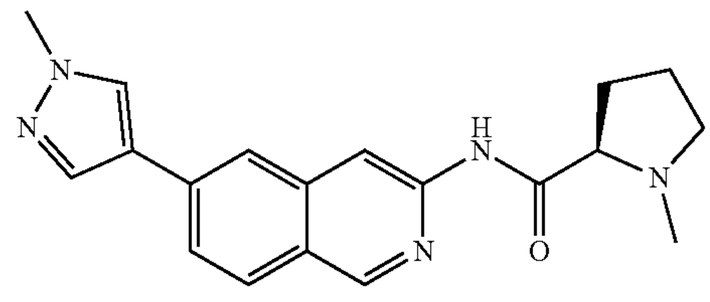
362



(R)—N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-1-oxotetrahydro-1H-pyrrolo[1,2-c]imidazole-2 (3H)-carboxamide 362

White solid (120.0 mg, 0.360 mmol, 57.8% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.70-1.83 (2H, m), 2.02 (1H, dtd, J=12.49, 8.16, 8.16, 3.84 Hz), 2.08-2.18 (1H, m), 2.64 (1H, td, J=9.33, 6.86 Hz), 3.17 (1H, ddd, J=9.74, 6.17, 4.12 Hz), 3.90 (3H, s), 3.96 (1H, dd, J=9.06, 4.12 Hz), 4.99-5.10 (2H, m), 7.80 (1H, dd, J=8.51, 1.65 Hz), 8.04 (1H, d, J=8.51 Hz), 8.11 (1H, s), 8.13 (1H, s), 8.38 (1H, s), 8.60 (1H, s), 9.09 (1H, s); ESIMS found for $C_{19}H_{19}N_5O$ m/z 334.1 (M+1).

363

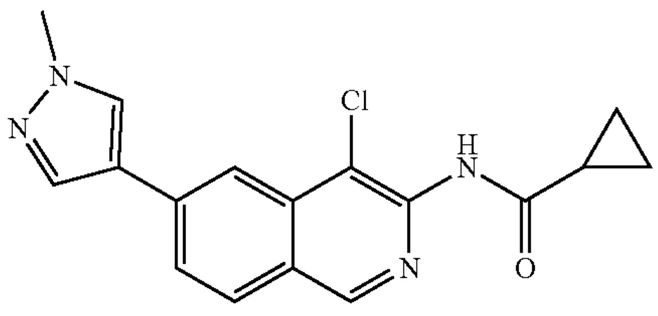


(R)-1-Methyl-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)pyrrolidine-2-carboxamide 363

Off-white solid (65.0 mg, 0.194 mmol, 62.3% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.74-1.82 (2H, m),

1.82-1.90 (1H, m), 2.17-2.28 (1H, m), 2.37-2.44 (1H, m), 2.42 (3H, s), 3.07 (1H, dd, J=9.88, 5.49 Hz), 3.17 (1H, ddd, J=8.92, 6.04, 3.16 Hz), 3.90 (3H, s), 7.77 (1H, dd, J=8.51, 1.65 Hz), 8.03 (1H, d, J=8.51 Hz), 8.10 (2H, s), 8.37 (1H, s), 8.44 (1H, s), 9.03 (1H, s), 9.92 (1H, s); ESIMS found for $C_{19}H_{21}N_5O$ m/z 336.2 (M+1).

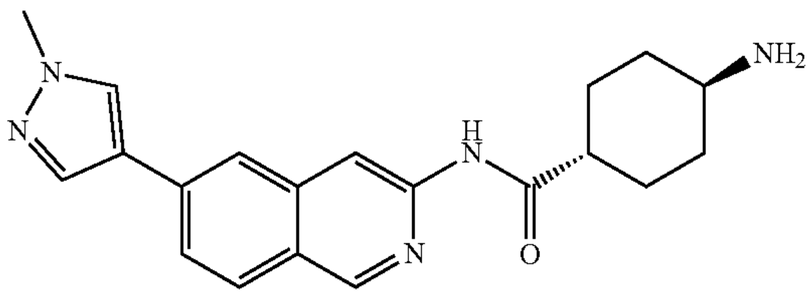
364



N-(4-Chloro-6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl) cyclopropanecarboxamide 364

Beige solid (240.0 mg, 0.734 mmol, 95.0% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 0.80-0.86 (4H, m), 1.91 (1H, quip, J=6.24 Hz), 3.92 (3H, s), 7.99 (1H, dd, J=8.51, 1.37 Hz), 8.14 (1H, s), 8.19 (1H, d, J=8.78 Hz), 8.22 (1H, d, J=0.82 Hz), 8.49 (1H, s), 9.10 (1H, s), 10.48 (1H, s); ESIMS found for $C_{17}H_{15}ClN_4O$ m/z 327.1 (M+1).

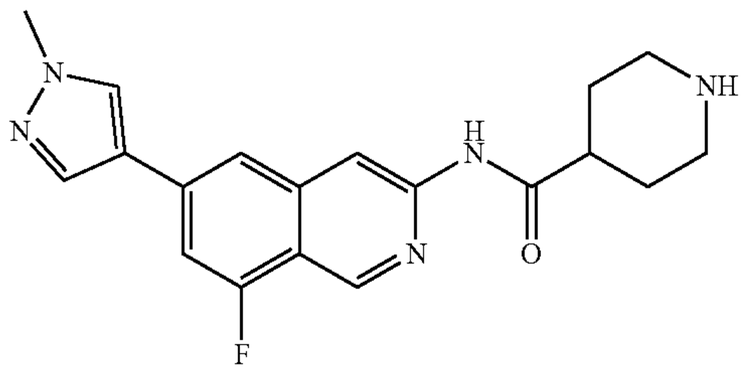
365



trans-4-Amino-N-(6-(1-methyl-1H-pyrazol-4-yl) isoquinolin-3-yl) cyclohexane-1-carboxamide 365

Beige solid (350.0 mg, 1.00 mmol, 90.1% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 0.99-1.11 (2H, m), 1.42-1.64 (4H, m), 1.82 (4H, br d, J=11.80 Hz), 2.42-2.49 (1H, m), 3.90 (3H, s), 7.74 (1H, dd, J=8.51, 1.65 Hz), 7.99 (1H, d, J=8.51 Hz), 8.02 (1H, s), 8.07 (1H, s), 8.35 (1H, s), 8.42 (1H, s), 9.02 (1H, s), 10.40 (1H, s); ESIMS found for $C_{20}H_{23}N_5O$ m/z 350.2 (M+1).

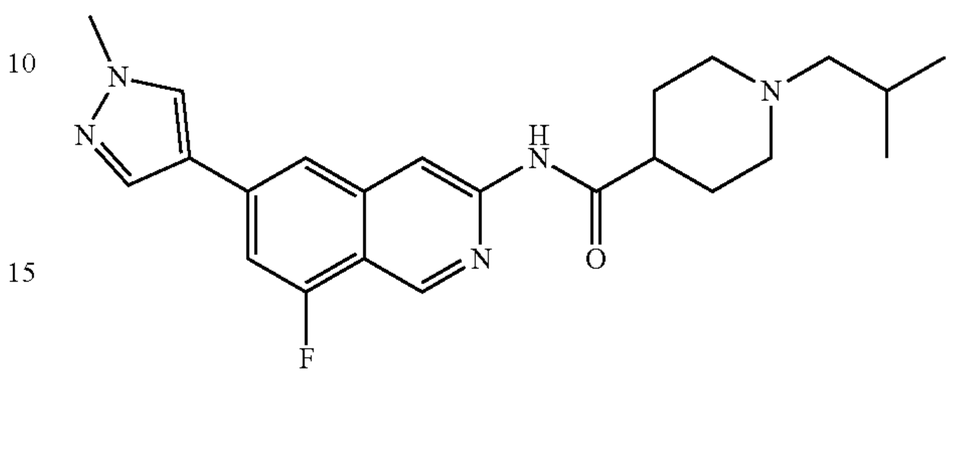
366



N-(8-Fluoro-6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)piperidine-4-carboxamide 366

White solid (260.0 mg, 0.736 mmol, 73.6% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.53 (2H, qd, J=12.21, 3.98 Hz), 1.70 (2H, br d, J=10.98 Hz), 2.42-2.49 (2H, m), 2.60-2.70 (1H, m), 2.97 (2H, br d, J=14.00 Hz), 3.90 (3H, s), 7.58 (1H, dd, J=12.08, 1.10 Hz), 7.92 (1H, s), 8.11 (1H, s), 8.39 (1H, s), 8.49 (1H, s), 9.14 (1H, s), 10.56 (1H, s); ESIMS found for $C_{19}H_{20}FN_5O$ m/z 354.15 (M+1).

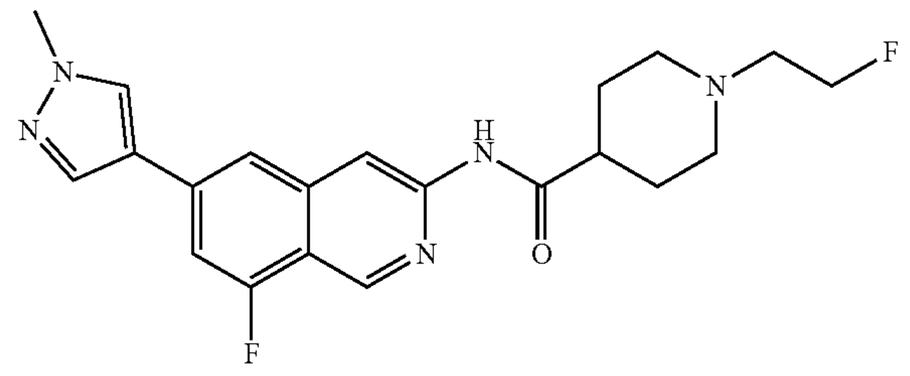
367



N-(8-Fluoro-6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-1-isobutylpiperidine-4-carboxamide 367

Beige solid (15.0 mg, 0.037 mmol, 16.2% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 0.86 (6H, d, J=6.59 Hz), 1.61-1.72 (2H, m), 1.73-1.81 (3H, m), 1.83-1.92 (2H, m), 2.02 (2H, d, J=7.41 Hz), 2.51-2.59 (1H, m), 2.82-2.91 (2H, m), 3.90 (3H, s), 7.58 (1H, dd, J=12.08, 1.10 Hz), 7.92 (1H, s), 8.11 (1H, s), 8.39 (1H, s), 8.49 (1H, s), 9.15 (1H, s), 10.61 (1H, s); ESIMS found for $C_{23}H_{28}FN_5O$ m/z 410.2 (M+1).

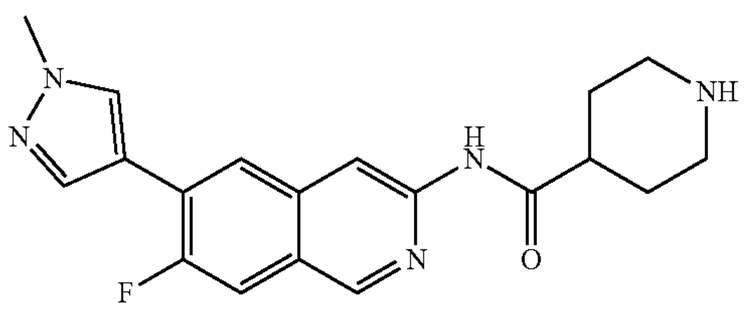
368



N-(8-Fluoro-6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-1-(2-fluoroethyl) piperidine-4-carboxamide 368

Off-white solid (26.0 mg, 0.065 mmol, 28.8% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.68 (2H, qd, J=12.21, 3.70 Hz), 1.75-1.83 (2H, m), 2.00-2.07 (2H, m), 2.52-2.57 (1H, m), 2.61 (2H, dt, J=28.30, 4.95 Hz), 2.94 (2H, br d, J=11.53 Hz), 3.90 (3H, s), 4.53 (2H, dt, J=48.10, 5.25 Hz), 7.59 (1H, dd, J=12.08, 1.37 Hz), 7.92 (1H, s), 8.11 (1H, d, J=0.82 Hz), 8.39 (1H, s), 8.50 (1H, s), 9.15 (1H, s), 10.62 (1H, s); ESIMS found for $C_{21}H_{23}F_2N_5O$ m/z 400.2 (M+1).

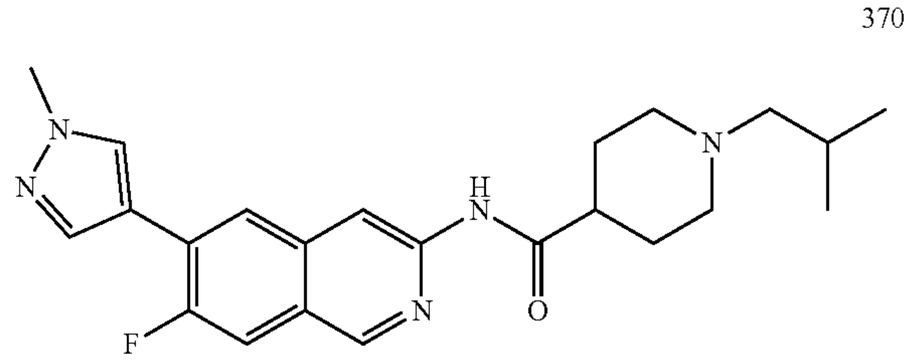
369



N-(7-Fluoro-6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)piperidine-4-carboxamide 369

Off-white solid (135.0 mg, 0.382 mmol, 74.0% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.53 (2H, qd, J=12.17, 3.84 Hz), 1.70 (2H, br dd, J=12.08, 1.65 Hz), 2.43-2.49 (2H, m), 2.63 (1H, tt, J=11.63, 3.74 Hz), 2.97 (2H, br d, J=12.08 Hz), 3.93 (3H, s), 7.89 (1H, d, J=11.80 Hz), 8.10 (1H, s), 8.26 (1H, d, J=7.41 Hz), 8.30 (1H, d, J=2.74 Hz), 8.49 (1H, s), 9.03 (1H, s), 10.44 (1H, s); ESIMS found for $C_{19}H_{20}FN_5O$ m/z 354.15 (M+1).

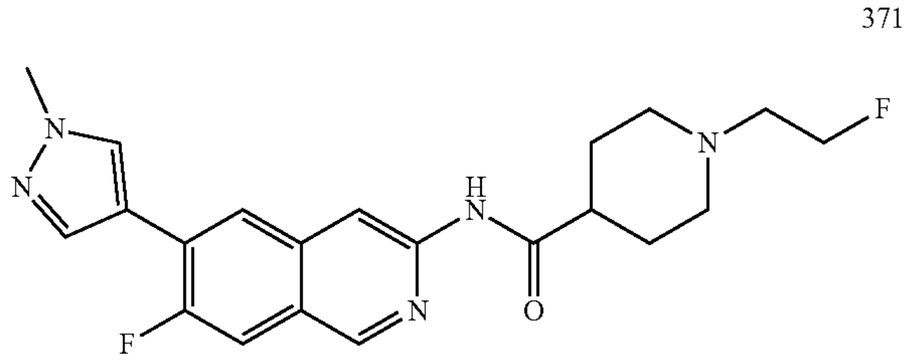
370



N-(7-Fluoro-6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-1-isobutylpiperidine-4-carboxamide 370

Off-white solid (45.0 mg, 0.106 mmol, 53.4% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 0.86 (6H, d, J=6.59 Hz), 1.61-1.72 (2H, m), 1.73-1.81 (3H, m), 1.83-1.92 (2H, m), 2.02 (2H, d, J=7.41 Hz), 2.51-2.58 (1H, m), 2.86 (2H, br d, J=11.25 Hz), 3.93 (3H, s), 7.89 (1H, d, J=11.53 Hz), 8.10 (1H, d, J=0.82 Hz), 8.27 (1H, d, J=7.41 Hz), 8.30 (1H, d, J=2.74 Hz), 8.50 (1H, s), 9.03 (1H, s), 10.49 (1H, s); ESIMS found for $C_{23}H_{28}FN_5O$ m/z 410.2 (M+1).

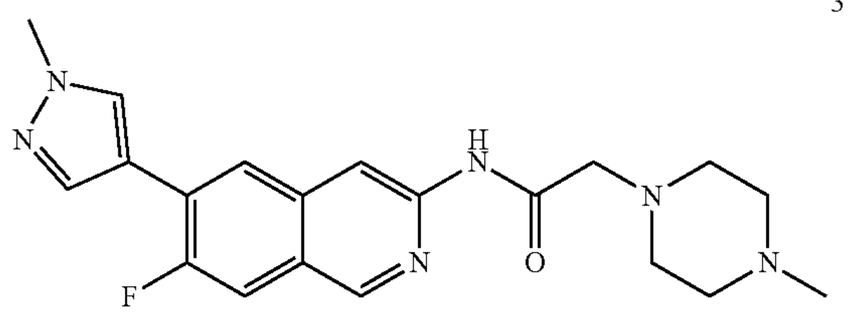
371



N-(7-Fluoro-6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-1-(2-fluoroethyl) piperidine-4-carboxamide 371

White solid (30.0 mg, 0.072 mmol, 51.1% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.68 (2H, qd, J=12.21, 3.70 Hz), 1.76-1.83 (2H, m), 2.04 (2H, td, J=11.80, 2.20 Hz), 2.54 (1H, td, J=7.62, 3.98 Hz), 2.61 (2H, dt, J=28.35, 4.95 Hz), 2.94 (2H, br d, J=11.53 Hz), 3.93 (3H, s), 4.53 (2H, dt, J=47.80, 4.95 Hz), 7.89 (1H, d, J=11.53 Hz), 8.10 (1H, s), 8.27 (1H, d, J=7.68 Hz), 8.30 (1H, d, J=2.74 Hz), 8.50 (1H, s), 9.04 (1H, s), 10.49 (1H, s); ESIMS found for $C_{21}H_{23}F_2N_5O$ m/z 400.2 (M+1).

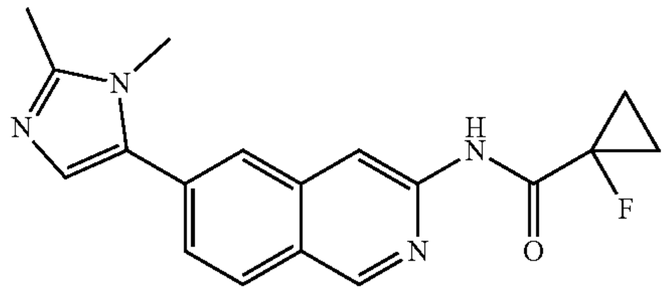
372



N-(7-Fluoro-6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(4-methylpiperazin-1-yl)acetamide 372

Off-white solid (16.0 mg, 0.042 mmol, 13.5% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 2.19 (3H, s), 2.40 (4H, br s), 2.58 (4H, br s), 3.22 (2H, s), 3.93 (3H, s), 7.92 (1H, d, J=11.53 Hz), 8.13 (1H, s), 8.32 (1H, d, J=3.02 Hz), 8.34 (1H, d, J=7.41 Hz), 8.49 (1H, s), 9.05 (1H, s), 9.95 (1H, s); ESIMS found for $C_{20}H_{23}FN_6O$ m/z 383.2 (M+1).

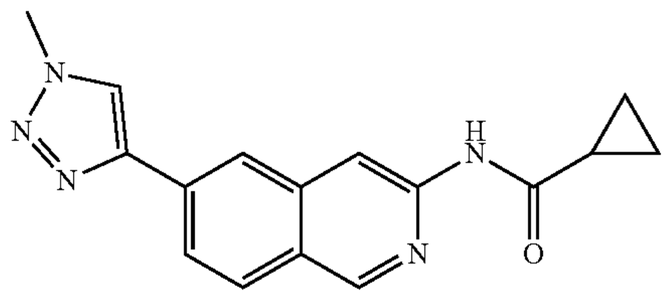
376



N-(6-(1,2-Dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-1-fluorocyclopropane-1-carboxamide 376

Beige solid (32.0 mg, 0.094 mmol, 19.3% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.33-1.42 (2H, m), 1.43-1.53 (2H, m), 2.39 (3H, s), 3.67 (3H, s), 7.13 (1H, s), 7.67 (1H, dd, J=8.51, 1.65 Hz), 7.97 (1H, s), 8.13 (1H, d, J=8.51 Hz), 8.46 (1H, s), 9.18 (1H, s), 10.28 (1H, s); ESIMS found for $C_{18}H_{17}FN_4O$ m/z 325.1 (M+1).

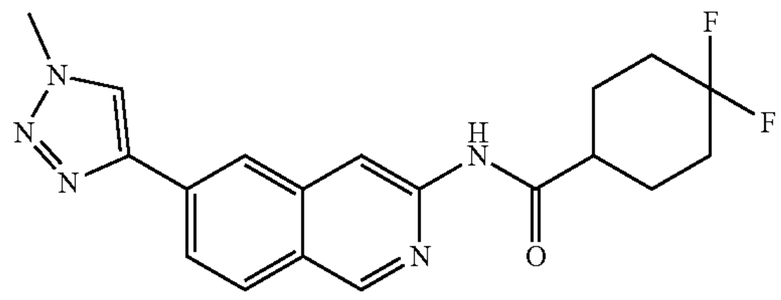
433



N-(6-(1-Methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl) cyclopropanecarboxamide 433

Beige solid (14.0 mg, 0.048 mmol, 10.8% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 0.79-0.91 (4H, m), 2.03-2.12 (1H, m), 4.14 (3H, s), 8.01 (1H, dd, J=8.51, 1.65 Hz), 8.11 (1H, d, J=8.78 Hz), 8.26 (1H, s), 8.47 (1H, s), 8.72 (1H, s), 9.12 (1H, s), 10.90 (1H, s); ESIMS found for $C_{16}H_{15}N_5O$ m/z 294.1 (M+1).

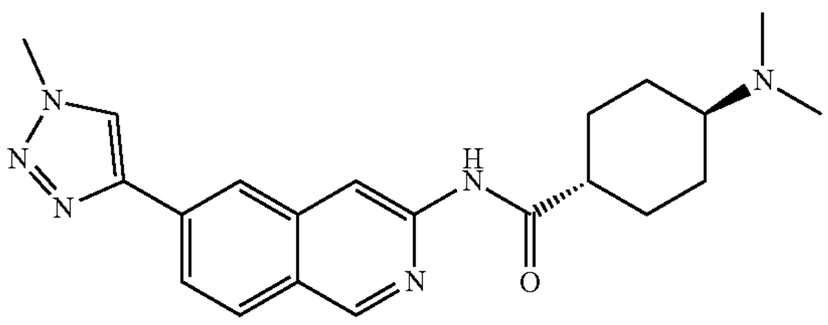
441



4,4-Difluoro-N-(6-(1-methyl-1H-1,2,3-triazol-4-yl) isoquinolin-3-yl) cyclohexane-1-carboxamide 441

White solid (57.8 mg, 0.156 mmol, 43.2% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.67-1.91 (4H, m), 1.96 (2H, br d, J=12.90 Hz), 2.08-2.18 (2H, m), 2.69-2.75 (1H, m), 4.14 (3H, s), 8.02 (1H, dd, J=8.51, 1.37 Hz), 8.11 (1H, d, J=8.51 Hz), 8.29 (1H, s), 8.50 (1H, s), 8.73 (1H, s), 9.12 (1H, s), 10.63 (1H, s); ESIMS found for $C_{19}H_{19}F_2N_5O$ m/z 372.2 (M+1).

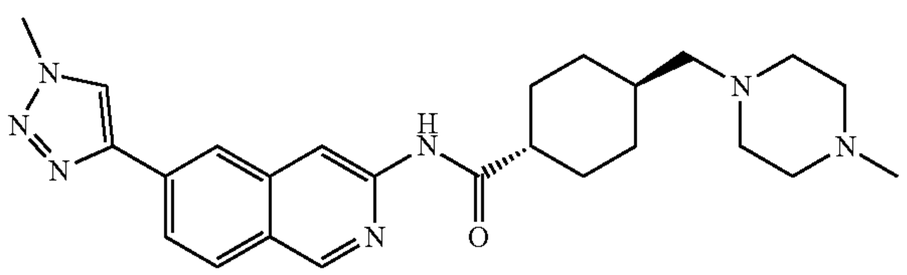
443



trans-4-(Dimethylamino)-N-(6-(1-methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)cyclohexane-1-carboxamide 443

White solid (8.0 mg, 0.021 mmol, 10.9% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.13-1.23 (2H, m), 1.43-1.55 (2H, m), 1.83-1.96 (4H, m), 2.11-2.16 (1H, m), 2.18 (6H, s), 2.44-2.48 (1H, m), 4.14 (3H, s), 8.01 (1H, dd, J=8.51, 1.65 Hz), 8.10 (1H, d, J=8.51 Hz), 8.27 (1H, s), 8.49 (1H, s), 8.72 (1H, s), 9.11 (1H, s), 10.47 (1H, s); ESIMS found for $C_{21}H_{26}N_6O$ m/z 379.2 (M+1).

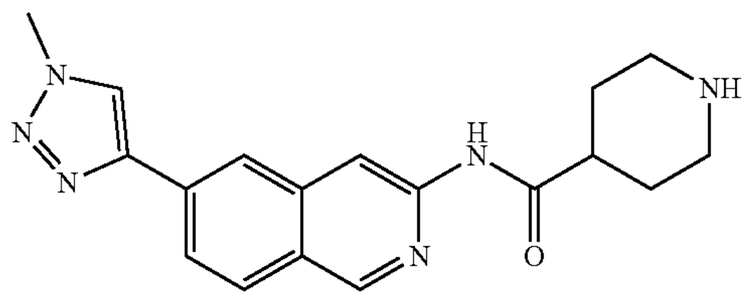
448



trans-N-(6-(1-Methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)-4-((4-methylpiperazin-1-yl)methyl)cyclohexane-1-carboxamide 448

Off-white solid (22.0 mg, 0.049 mmol, 14.6% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 0.82-0.95 (2H, m), 1.41-1.52 (3H, m), 1.79-1.91 (4H, m), 2.08 (2H, d, J=7.14 Hz), 2.14 (3H, s), 2.31 (8H, br s), 2.51-2.55 (1H, m), 4.14 (3H, s), 8.00 (1H, dd, J=8.51, 1.37 Hz), 8.10 (1H, d, J=8.51 Hz), 8.27 (1H, s), 8.50 (1H, s), 8.72 (1H, s), 9.10 (1H, s), 10.47 (1H, s); ESIMS found for $C_{25}H_{33}N_7O$ m/z 448.3 (M+1).

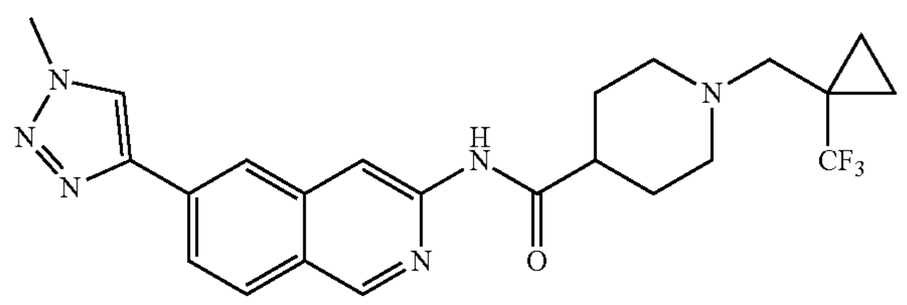
452



N-(6-(1-Methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)piperidine-4-carboxamide 452

White solid (119.4 mg, 0.355 mmol, 77.9% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.54 (2H, qd, J=12.17, 3.84 Hz), 1.71 (2H, br d, J=11.25 Hz), 2.45-2.49 (2H, m), 2.65 (1H, tt, J=11.70, 3.67 Hz), 2.98 (2H, br d, J=12.08 Hz), 4.14 (3H, s), 8.01 (1H, dd, J=8.51, 1.37 Hz), 8.11 (1H, d, J=8.51 Hz), 8.28 (1H, s), 8.50 (1H, s), 8.73 (1H, s), 9.11 (1H, s), 10.48 (1H, s); ESIMS found for $C_{18}H_{20}N_6O$ m/z 337.2 (M+1).

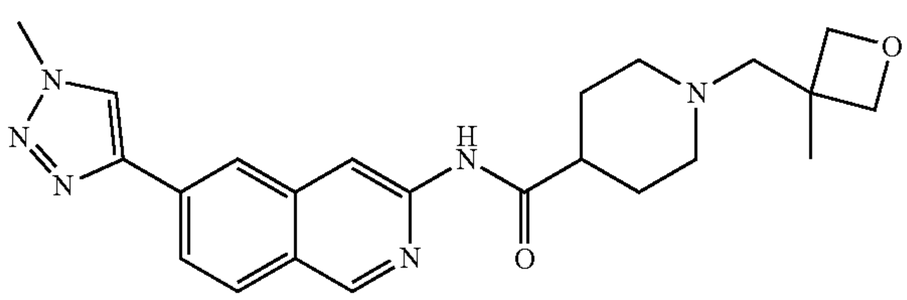
470



N-(6-(1-Methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)-1-((1-(trifluoromethyl)cyclopropyl)methyl)piperidine-4-carboxamide 470

White solid (75.9 mg, 0.166 mmol, 79.4% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 0.73 (2H, br s), 0.93-1.00 (2H, m), 1.63-1.74 (2H, m), 1.78 (2H, br d, J=10.70 Hz), 1.95 (2H, br t, J=10.57 Hz), 2.52-2.60 (1H, m), 2.97 (2H, br d, J=10.98 Hz), 3.28 (2H, s), 4.14 (3H, s), 8.01 (1H, dd, J=8.51, 1.37 Hz), 8.11 (1H, d, J=8.51 Hz), 8.28 (1H, s), 8.50 (1H, s), 8.72 (1H, s), 9.11 (1H, s), 10.52 (1H, s); ESIMS found for $C_{23}H_{25}F_3N_6O$ m/z 459.2 (M+1).

472

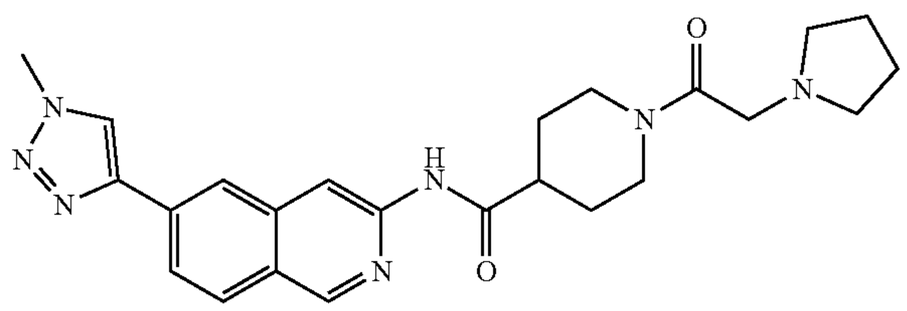


N-(6-(1-Methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)-1-((3-methyloxetan-3-yl)methyl)piperidine-4-carboxamide 472

Beige solid (32.0 mg, 0.076 mmol, 21.1% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.31 (3H, s), 1.60-1.71

(2H, m), 1.72-1.80 (2H, m), 1.93-2.02 (2H, m), 2.48 (2H, br s), 2.52-2.59 (1H, m), 2.59-2.67 (2H, m), 4.14 (3H, s), 4.19 (2H, d, J=5.49 Hz), 4.36 (2H, d, J=5.76 Hz), 8.01 (1H, dd, J=8.51, 1.37 Hz), 8.11 (1H, d, J=8.51 Hz), 8.28 (1H, s), 8.50 (1H, s), 8.73 (1H, s), 9.11 (1H, s), 10.54 (1H, s); ESIMS found for $C_{23}H_{28}N_6O_2$ m/z 421.2 (M+1).

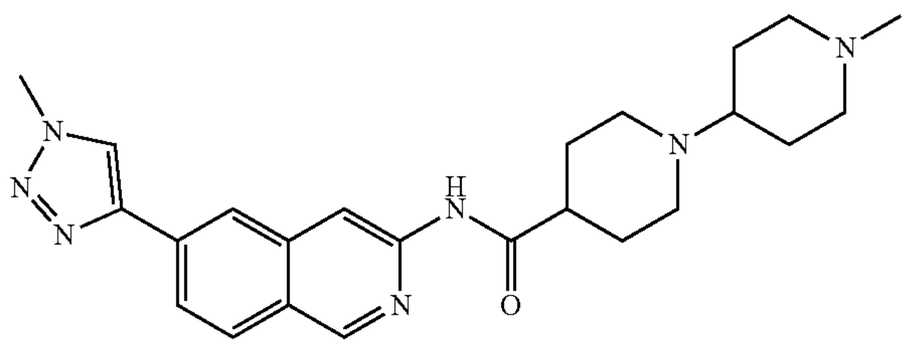
475



N-(6-(1-Methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)-1-(2-(pyrrolidin-1-yl) acetyl)piperidine-4-carboxamide 475

White solid (7.8 mg, 0.017 mmol, 20.5% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.44-1.55 (2H, m), 1.57-1.66 (2H, m), 1.67-1.73 (4H, m), 1.85 (2H, br d, J=10.43 Hz), 2.58-2.65 (1H, m), 2.82 (1H, ddd, J=11.32, 7.34, 4.39 Hz), 2.99-3.06 (1H, m), 3.16-3.21 (2H, m), 3.30-3.38 (2H, m), 4.10 (1H, br d, J=1.10 Hz), 4.14 (3H, s), 4.36-4.44 (1H, m), 8.01 (1H, dd, J=8.51, 1.37 Hz), 8.11 (1H, d, J=8.78 Hz), 8.28 (1H, s), 8.49 (1H, s), 8.71 (1H, s), 9.11 (1H, s), 10.56 (1H, s); ESIMS found for $C_{24}H_{29}N_7O_2$ m/z 448.0 (M+1).

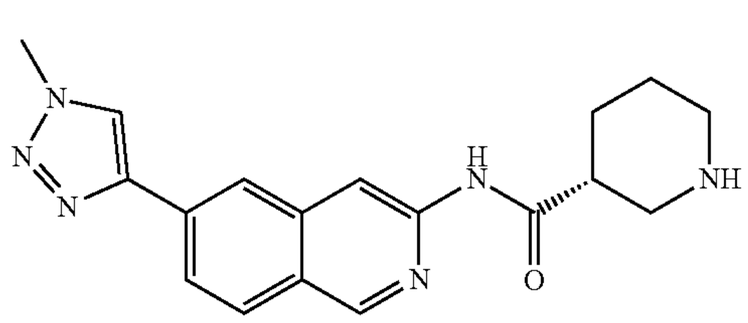
477



1'-Methyl-N-(6-(1-methyl-1H-1,2,3-triazol-4-yl) isoquinolin-3-yl)-[1,4'-bipiperidine]-4-carboxamide 477

Off-white solid (65.0 mg, 0.150 mmol, 37.6% yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.43 (2H, qd, J=11.94, 3.70 Hz), 1.57-1.70 (4H, m), 1.75-1.86 (4H, m), 2.08-2.19 (1H, m), 2.12 (3H, s), 2.51-2.57 (1H, m), 2.77 (2H, br d, J=11.53 Hz), 2.90 (2H, br d, J=11.25 Hz), 3.17 (2H, d, J=2.20 Hz), 4.14 (3H, s), 8.01 (1H, dd, J=8.51, 1.65 Hz), 8.10 (1H, d, J=8.51 Hz), 8.28 (1H, s), 8.51 (1H, s), 8.72 (1H, s), 9.10 (1H, s), 10.51 (1H, s); ESIMS found for $C_{24}H_{31}N_7O$ m/z 434.25 (M+1).

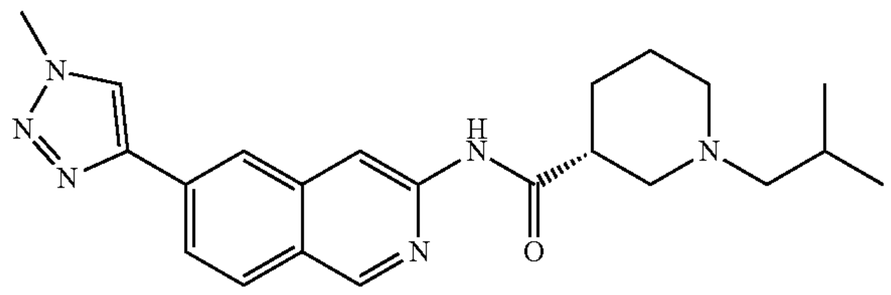
481



(R)—N-(6-(1-Methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)piperidine-3-carboxamide 481

White solid (80.4 mg, 0.239 mmol, 87.7% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.36-1.46 (1H, m), 1.56-1.64 (1H, m), 1.64-1.72 (1H, m), 1.84-1.92 (1H, m), 2.53-2.60 (1H, m), 2.63 (1H, dq, J=8.71, 4.41 Hz), 2.75 (1H, dd, J=11.94, 8.92 Hz), 2.81 (1H, dt, J=12.14, 3.95 Hz), 3.00 (1H, dd, J=11.94, 3.16 Hz), 4.14 (3H, s), 8.01 (1H, dd, J=8.51, 1.65 Hz), 8.11 (1H, d, J=8.51 Hz), 8.28 (1H, s), 8.49 (1H, s), 8.73 (1H, s), 9.10 (1H, s), 10.81 (1H, s); ESIMS found for $C_{18}H_{20}N_6O$ m/z 337.2 (M+1).

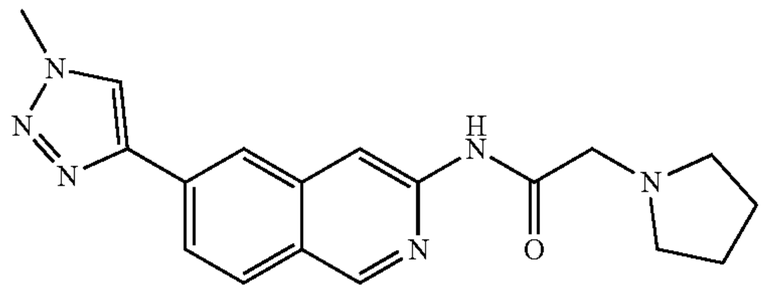
483



(R)-1-Isobutyl-N-(6-(1-methyl-1H-1,2,3-triazol-4-yl) isoquinolin-3-yl) piperidine-3-carboxamide 483

White solid (45.9 mg, 0.117 mmol, 82.3% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 0.88 (3H, d, J=6.59 Hz), 0.91 (3H, d, J=6.59 Hz), 1.50-1.61 (2H, m), 1.65-1.73 (1H, m), 1.78-1.86 (2H, m), 2.08 (2H, br d, J=7.41 Hz), 2.10-2.16 (1H, m), 2.25-2.33 (1H, m), 2.55-2.62 (1H, m), 2.77 (2H, br d, J=7.68 Hz), 4.14 (3H, s), 8.01 (1H, dd, J=8.51, 1.65 Hz), 8.11 (1H, d, J=8.78 Hz), 8.28 (1H, s), 8.49 (1H, s), 8.73 (1H, s), 9.10 (1H, s), 10.73 (1H, s); ESIMS found for $C_{22}H_{28}N_6O$ m/z 393.2 (M+1).

487

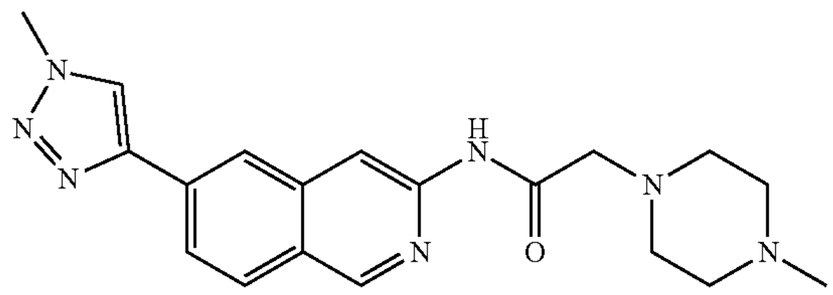


N-(6-(1-Methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)-2-(pyrrolidin-1-yl) acetamide 487

Off-white solid (18.2 mg, 0.054 mmol, 16.0% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.78 (4H, dt, J=6.52, 3.19 Hz), 2.62-2.70 (4H, m), 3.36 (2H, s), 4.14 (3H, s), 8.04 (1H, dd, J=8.51, 1.37 Hz), 8.13 (1H, d, J=8.51 Hz), 8.34

(1H, s), 8.50 (1H, s), 8.74 (1H, s), 9.12 (1H, s), 9.98 (1H, s); ESIMS found for $C_{18}H_{20}N_6O$ m/z 337.15 (M+1).

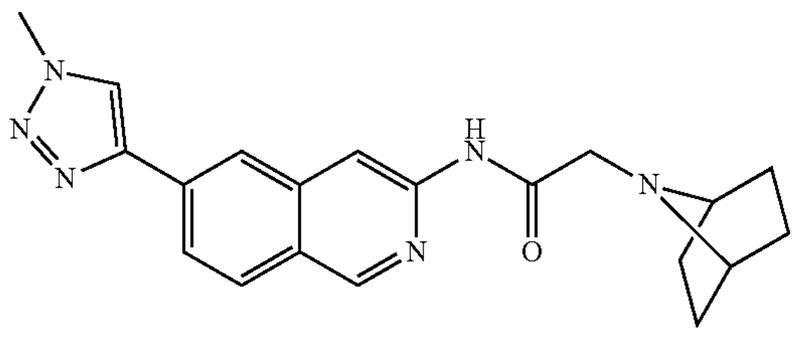
500



N-(6-(1-Methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)-2-(4-methylpiperazin-1-yl)acetamide 500

Beige solid (5.0 mg, 0.014 mmol, 4.1% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 2.19 (3H, s), 2.34-2.46 (4H, m), 2.58 (4H, br s), 3.23 (2H, s), 4.14 (3H, s), 8.04 (1H, dd, J=8.51, 1.65 Hz), 8.14 (1H, d, J=8.51 Hz), 8.34 (1H, s), 8.50 (1H, s), 8.74 (1H, s), 9.13 (1H, s), 10.00 (1H, s); ESIMS found for $C_{19}H_{23}N_7O$ m/z 366.2 (M+1).

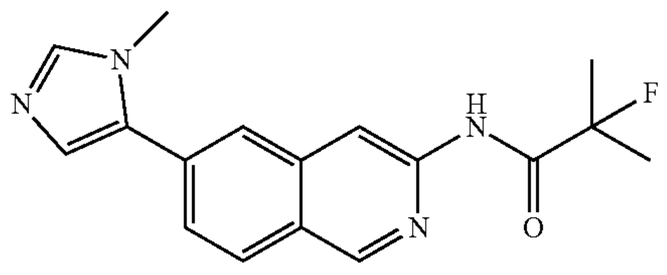
513



2-(7-Azabicyclo[2.2.1]heptan-7-yl)-N-(6-(1-methyl-1H-1,2,3-triazol-4-yl) isoquinolin-3-yl)acetamide 513

White solid (12.2 mg, 0.034 mmol, 17.8% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.34 (4H, br d, J=7.14 Hz), 1.75 (4H, br d, J=6.86 Hz), 3.20 (2H, s), 3.37 (2H, br s), 4.14 (3H, s), 8.05 (1H, dd, J=8.51, 1.37 Hz), 8.14 (1H, d, J=8.51 Hz), 8.35 (1H, s), 8.52 (1H, s), 8.74 (1H, s), 9.12 (1H, s), 10.14 (1H, s); ESIMS found for $C_{20}H_{22}N_6O$ m/z 363.2 (M+1).

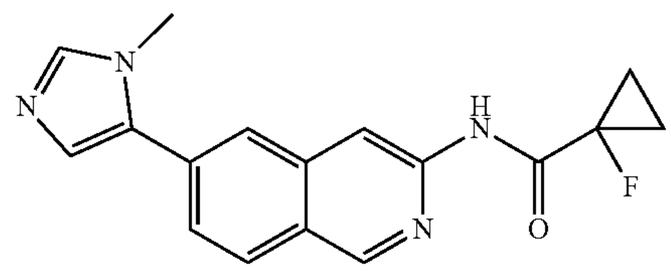
517



2-Fluoro-2-methyl-N-(6-(1-methyl-1H-imidazol-5-yl)isoquinolin-3-yl) propanamide 517

Off-white solid (70.0 mg, 0.224 mmol, 50.3% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.64 (6H, d, J=21.70 Hz), 3.83 (3H, s), 7.32 (1H, d, J=1.10 Hz), 7.73 (1H, dd, J=8.51, 1.65 Hz), 7.79 (1H, s), 8.07 (1H, s), 8.14 (1H, d, J=8.51 Hz), 8.49 (1H, s), 9.18 (1H, s), 9.85 (1H, br d, J=3.57 Hz);ESIMS found for $C_{17}H_{17}FN_4O$ m/z 313.0 (M+1).

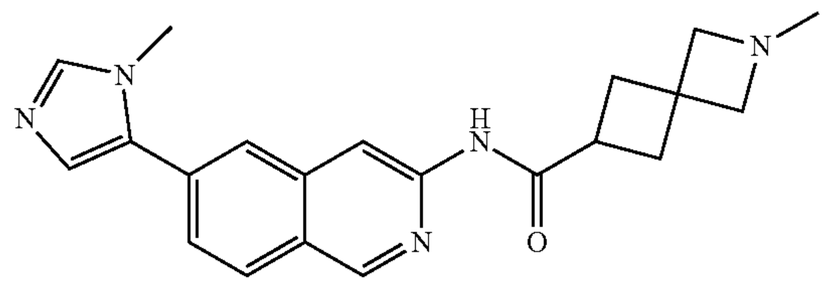
521



1-Fluoro-N-(6-(1-methyl-1H-imidazol-5-yl)isoquinolin-3-yl)cyclopropane-1-carboxamide 521

White solid (100.0 mg, 0.306 mmol, 63.1% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.34-1.42 (2H, m), 1.42-1.52 (2H, m), 3.83 (3H, s), 7.38 (1H, br s), 7.73 (1H, br d, J=8.51 Hz), 7.86 (1H, br s), 8.06 (1H, s), 8.14 (1H, d, J=8.51 Hz), 8.47 (1H, s), 9.19 (1H, s), 10.29 (1H, s); ESIMS found for $C_{17}H_{15}FN_4O$ m/z 311.1 (M+1).

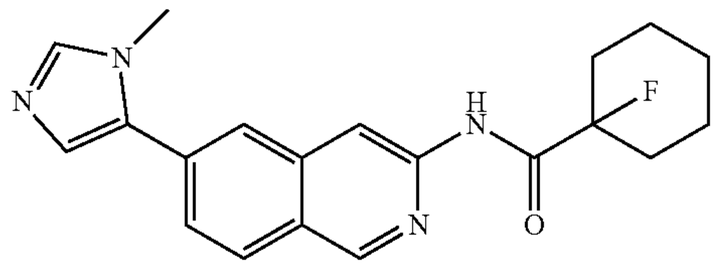
523



2-Methyl-N-(6-(1-methyl-1H-imidazol-5-yl)isoquinolin-3-yl)-2-azaspiro[3.3] heptane-6-carboxamide 523

White solid (5.0 mg, 0.014 mmol, 7.1% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 2.15 (3H, s), 2.22-2.36 (4H, m), 3.04 (2H, s), 3.14 (2H, s), 3.22-3.29 (1H, m), 3.83 (3H, s), 7.30 (1H, d, J=1.10 Hz), 7.66 (1H, dd, J=8.51, 1.65 Hz), 7.79 (1H, s), 8.00 (1H, s), 8.08 (1H, d, J=8.51 Hz), 8.54 (1H, s), 9.11 (1H, s), 10.42 (1H, s); ESIMS found for $C_{21}H_{23}N_5O$ m/z 362.2 (M+1).

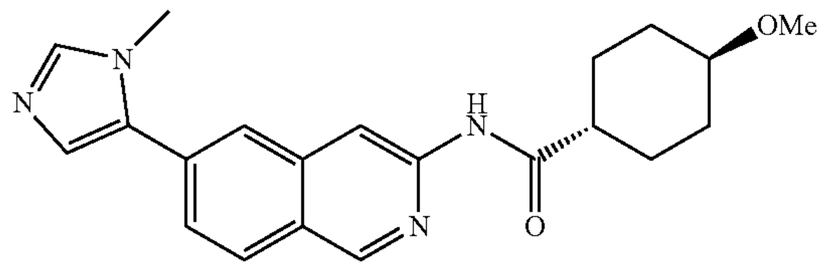
527



1-Fluoro-N-(6-(1-methyl-1H-imidazol-5-yl)isoquinolin-3-yl)cyclohexane-1-carboxamide 527

White solid (16.0 mg, 0.043 mmol, 10.1% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.30-1.42 (1H, m), 1.50-1.63 (2H, m), 1.68 (3H, br d, J=9.61 Hz), 1.85-2.02 (4H, m), 3.84 (3H, s), 7.32 (1H, d, J=1.10 Hz), 7.73 (1H, dd, J=8.51, 1.92 Hz), 7.80 (1H, s), 8.07 (1H, s), 8.13 (1H, d, J=8.51 Hz), 8.50 (1H, s), 9.17 (1H, s), 9.83 (1H, d, J=4.12 Hz); ESIMS found for $C_{20}H_{21}FN_4O$ m/z 353.15 (M+1).

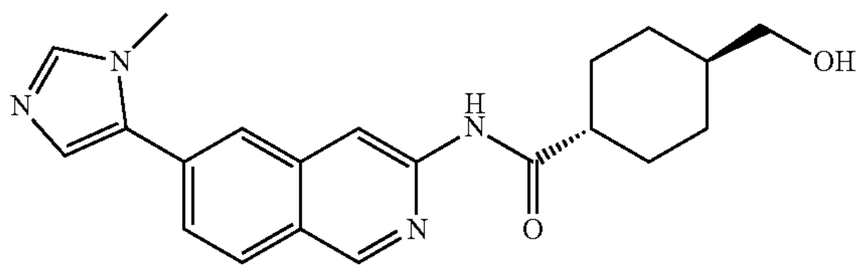
528



trans-4-Methoxy-N-(6-(1-methyl-1H-imidazol-5-yl) isoquinolin-3-yl) cyclohexane-1-carboxamide 528

White solid (96.6 mg, 0.265 mmol, 39.6% yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.06-1.18 (2H, m), 1.44-1.56 (2H, m), 1.86-1.95 (2H, m), 2.04-2.12 (2H, m), 2.52-2.58 (1H, m), 3.07-3.16 (1H, m), 3.25 (3H, s), 3.82 (3H, s), 7.30 (1H, s), 7.66 (1H, dd, J=8.51, 1.65 Hz), 7.79 (1H, s), 7.99 (1H, s), 8.08 (1H, d, J=8.51 Hz), 8.52 (1H, s), 9.12 (1H, s), 10.50 (1H, s); ESIMS found for $C_{21}H_{24}N_4O_2$ m/z 365.2 (M+1).

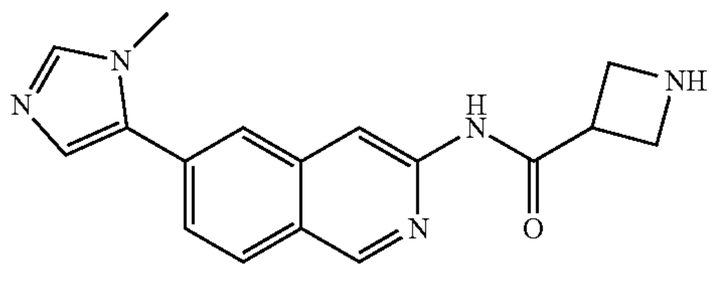
531



trans-4-(Hydroxymethyl)-N-(6-(1-methyl-1H-imidazol-5-yl)isoquinolin-3-yl)cyclohexane-1-carboxamide 531

Off-white solid (17.0 mg, 0.047 mmol, 7.0% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 0.95 (2H, qd, J=12.81, 3.29 Hz), 1.36 (1H, dtt, J=14.75, 5.90, 5.90, 3.05, 3.05 Hz), 1.45 (2H, qd, J=12.76, 3.16 Hz), 1.80 (2H, br dd, J=13.04, 2.61 Hz), 1.84-1.93 (2H, m), 2.51-2.54 (1H, m), 3.24 (2H, t, J=5.76 Hz), 3.82 (3H, s), 4.38 (1H, t, J=5.35 Hz), 7.30 (1H, d, J=1.10 Hz), 7.66 (1H, dd, J=8.51, 1.65 Hz), 7.79 (1H, s), 7.98 (1H, d, J=0.82 Hz), 8.08 (1H, d, J=8.51 Hz), 8.53 (1H, s), 9.12 (1H, s), 10.47 (1H, s); ESIMS found for $C_{21}H_{24}N_4O_2$ m/z 365.2 (M+1).

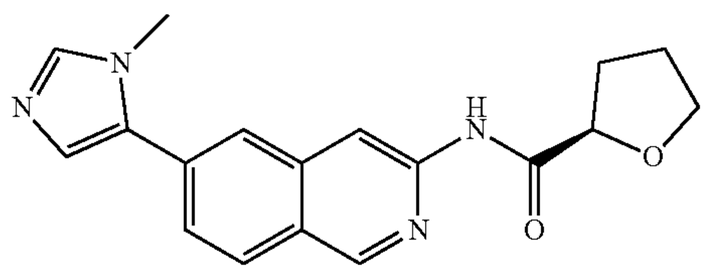
535



N-(6-(1-Methyl-1H-imidazol-5-yl)isoquinolin-3-yl) azetidine-3-carboxamide 535

Orange solid (4.0 mg, 0.013 mmol, 3.5% yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 3.23-3.32 (1H, m), 3.70-3.78 (2H, m), 3.83 (3H, s), 3.90-3.98 (2H, m), 7.31 (1H, d, J=1.10 Hz), 7.69 (1H, dd, J=8.51, 1.65 Hz), 7.80 (1H, s), 8.03 (1H, s), 8.10 (1H, d, J=8.51 Hz), 8.57 (1H, s), 9.13 (1H, s), 10.65 (1H, br s) ESIMS found for $C_{17}H_{17}N_5O$ m/z 308.15 (M+1).

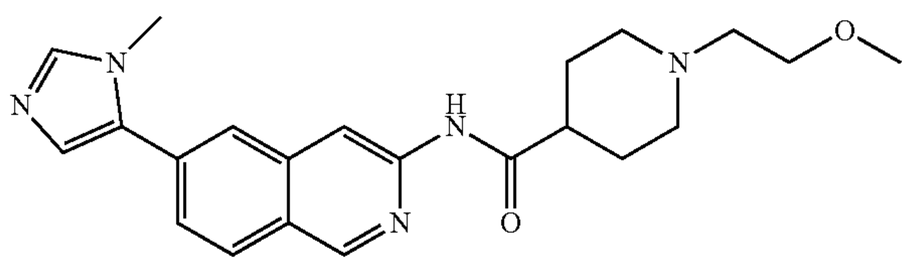
537



(R)—N-(6-(1-Methyl-1H-imidazol-5-yl)isoquinolin-3-yl)tetrahydrofuran-2-carboxamide 537

Off-white solid (100.0 mg, 0.310 mmol, 69.6% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.84-1.97 (2H, m), 1.98-2.08 (1H, m), 2.20-2.31 (1H, m), 3.83 (3H, s), 3.84-3.90 (1H, m), 4.00-4.07 (1H, m), 4.54 (1H, dd, J=8.23, 5.76 Hz), 7.31 (1H, d, J=0.82 Hz), 7.70 (1H, dd, J=8.51, 1.65 Hz), 7.79 (1H, s), 8.05 (1H, s), 8.11 (1H, d, J=8.51 Hz), 8.52 (1H, s), 9.14 (1H, s), 9.79 (1H, s); ESIMS found for $C_{18}H_{18}N_4O_2$ m/z 323.0 (M+1).

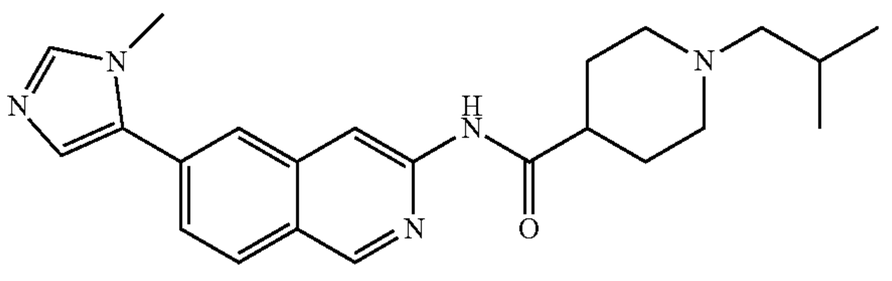
547



1-(2-Methoxyethyl)-N-(6-(1-methyl-1H-imidazol-5-yl)isoquinolin-3-yl) piperidine-4-carboxamide 547

Yellow-white solid (5.0 mg, 0.013 mmol, 8.5% yield). ^{1}H NMR (499 MHz, METHANOL-d_4) δ ppm 1.88-1.98 (4H, m), 2.25 (2H, dt, J=11.05, 7.51 Hz), 2.56 (1H, dt, J=15.51, 7.62 Hz), 2.66 (2H, t, J=5.63 Hz), 3.12 (2H, br d, J=11.80 Hz), 3.36 (3H, s), 3.57 (2H, t, J=5.63 Hz), 3.85 (3H, s), 7.28 (1H, s), 7.64 (1H, dd, J=8.51, 1.65 Hz), 7.85 (1H, s), 7.94 (1H, s), 8.07 (1H, d, J=8.51 Hz), 8.51 (1H, s), 9.06 (1H, s); ESIMS found for $C_{22}H_{27}N_5O_2$ m/z 394.2 (M+1).

554

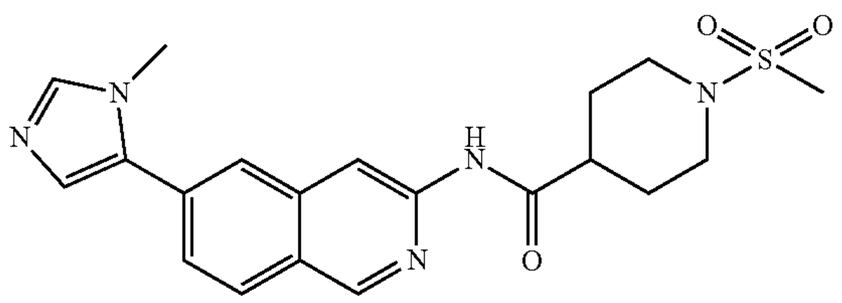


1-Isobutyl-N-(6-(1-methyl-1H-imidazol-5-yl)isoquinolin-3-yl)piperidine-4-carboxamide 554

White solid (50.0 mg, 0.121 mmol, 31.6% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 0.85 (6H, d, J=6.59 Hz), 1.60-1.73 (2H, m), 1.74-1.81 (3H, m), 1.83-1.91 (2H, m), 2.02 (2H, d, J=7.41 Hz), 2.52-2.60 (1H, m), 2.86 (2H, br d,

J=11.25 Hz), 3.83 (3H, s), 7.30 (1H, d, J=1.10 Hz), 7.66 (1H, dd, J=8.51, 1.65 Hz), 7.79 (1H, s), 8.00 (1H, s), 8.08 (1H, d, J=8.78 Hz), 8.54 (1H, s), 9.12 (1H, s), 10.52 (1H, s); ESIMS found for $C_{23}H_{29}N_5O$ m/z 392.2 (M+1).

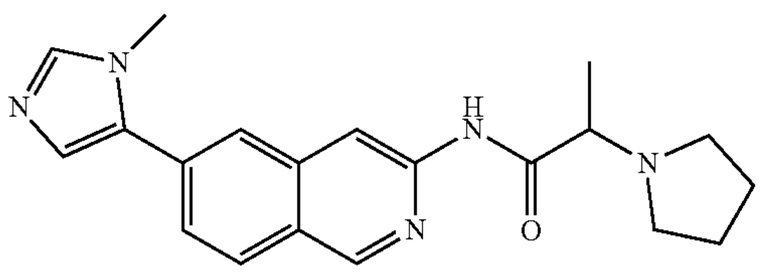
561



N-(6-(1-Methyl-1H-imidazol-5-yl)isoquinolin-3-yl)-1-(methylsulfonyl) piperidine-4-carboxamide 561

Beige solid (15.0 mg, 0.036 mmol, 21.7% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.64-1.77 (2H, m), 1.91-1.98 (2H, m), 2.65-2.73 (1H, m), 2.77 (2H, td, J=11.94, 2.20 Hz), 2.89 (3H, s), 3.59-3.67 (2H, m), 3.83 (3H, s), 7.30 (1H, d, J=1.10 Hz), 7.67 (1H, dd, J=8.64, 1.51 Hz), 7.78 (1H, s), 8.01 (1H, s), 8.09 (1H, d, J=8.51 Hz), 8.54 (1H, s), 9.13 (1H, s), 10.62 (1H, s); ESIMS found for $C_{20}H_{23}N_5O_3S$ m/z 413.9 (M+1).

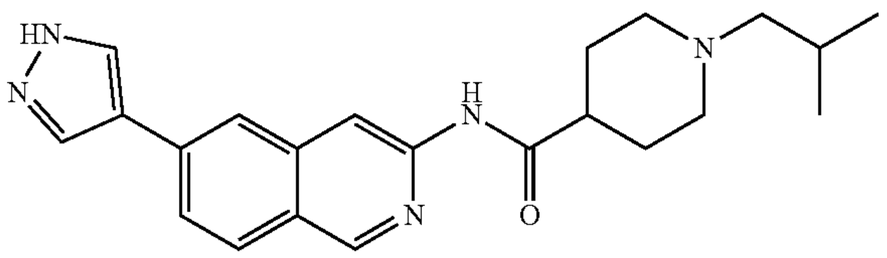
579



N-(6-(1-Methyl-1H-imidazol-5-yl)isoquinolin-3-yl)-2-(pyrrolidin-1-yl) propanamide 579

White solid (15.0 mg, 0.043 mmol, 10.6% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.30 (3H, d, J=6.86 Hz), 1.74 (4H, br s), 2.56-2.69 (4H, m), 3.28-3.31 (1H, m), 3.83 (3H, s), 7.31 (1H, s), 7.69 (1H, dd, J=8.51, 1.65 Hz), 7.80 (1H, s), 8.04 (1H, s), 8.10 (1H, d, J=8.51 Hz), 8.53 (1H, s), 9.13 (1H, s), 10.02 (1H, s); ESIMS found for $C_{20}H_{23}N_5O$ m/z 350.2 (M+1).

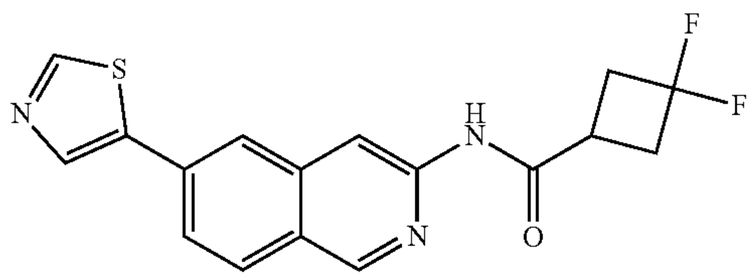
643



N-(6-(1H-Pyrazol-4-yl)isoquinolin-3-yl)-1-isobutylpiperidine-4-carboxamide 643

Brown solid (31.0 mg, 0.082 mmol, 32.1% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 0.86 (6H, d, J=6.59 Hz), 1.62-1.73 (2H, m), 1.73-1.80 (3H, m), 1.82-1.91 (2H, m), 2.02 (2H, d, J=7.41 Hz), 2.51-2.59 (1H, m), 2.86 (2H, br d, J=11.25 Hz), 7.80 (1H, dd, J=8.64, 1.51 Hz), 7.99 (1H, d, J=8.51 Hz), 8.09 (1H, s), 8.14 (1H, br s), 8.42 (1H, br s), 8.45 (1H, s), 9.02 (1H, s), 10.44 (1H, s), 13.09 (1H, br s); ESIMS found for $C_{22}H_{27}N_5O$ m/z 378.2 (M+1).

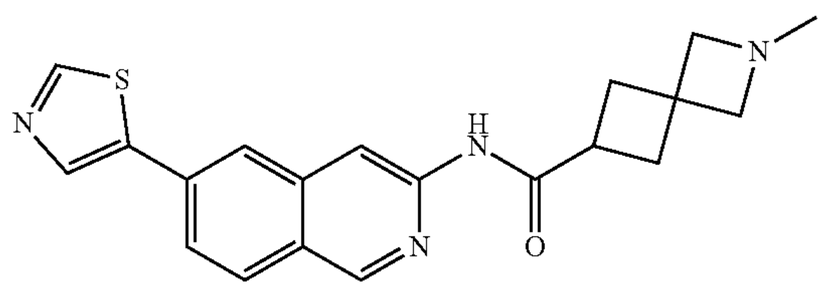
699



3,3-Difluoro-N-(6-(thiazol-5-yl)isoquinolin-3-yl) cyclobutane-1-carboxamide 699

Beige solid (8.0 mg, 0.023 mmol, 8.5% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 2.75-2.90 (5H, m), 7.89 (1H, dd, J=8.64, 1.78 Hz), 8.12 (1H, d, J=8.51 Hz), 8.24 (1H, s), 8.56 (1H, s), 8.57 (1H, s), 9.14 (1H, s), 9.20 (1H, s), 10.82 (1H, s); ESIMS found for $C_{17}H_{13}F_2N_3OS$ m/z 346.05 (M+1).

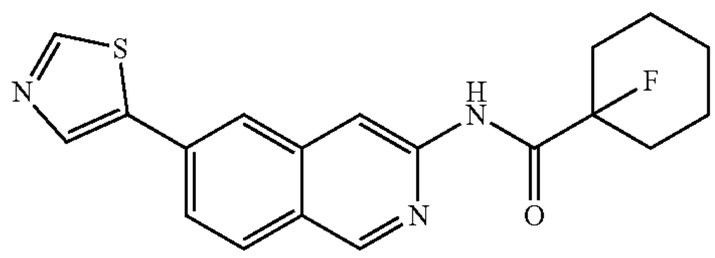
700



2-Methyl-N-(6-(thiazol-5-yl)isoquinolin-3-yl)-2-azaspiro[3.3]heptane-6-carboxamide 700

Beige solid (4.0 mg, 0.011 mmol, 12.8% yield). ^{1}H NMR (499 MHz, METHANOL-d_4) δ ppm 2.39 (3H, s), 2.42-2.55 (4H, m), 3.22-3.29 (1H, m), 3.41 (2H, s), 3.48 (2H, s), 7.83 (1H, dd, J=8.51, 1.65 Hz), 8.05 (1H, d, J=8.51 Hz), 8.11 (1H, d, J=0.82 Hz), 8.40 (1H, s), 8.50 (1H, s), 9.02 (1H, s), 9.06 (1H, s); ESIMS found for $C_{20}H_{20}N_4OS$ m/z 365.1 (M+1).

704

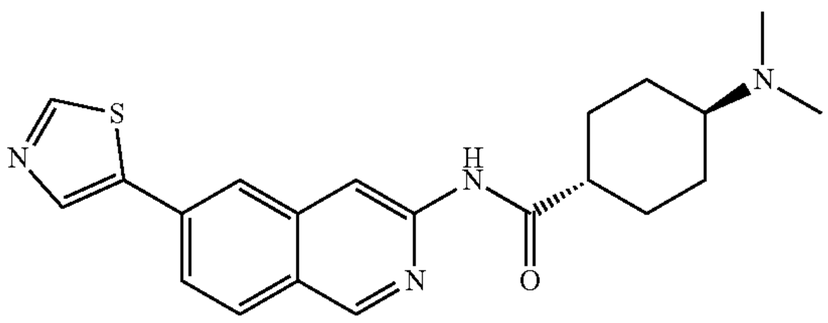


1-Fluoro-N-(6-(thiazol-5-yl)isoquinolin-3-yl)cyclohexane-1-carboxamide 704

Light pink solid (14.0 mg, 0.039 mmol, 17.9% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.28-1.42 (1H, m), 1.49-1.62 (2H, m), 1.68 (3H, br d, J=9.61 Hz), 1.85-2.02 (4H, m), 7.93 (1H, dd, J=8.64, 1.78 Hz), 8.15 (1H, d, J=8.78

Hz), 8.28 (1H, s), 8.49 (1H, s), 8.58 (1H, s), 9.18 (1H, s), 9.20 (1H, s), 9.87 (1H, d, J=4.12 Hz); ESIMS found for $C_{19}H_{18}FN_3OS$ m/z 355.9 (M+1).

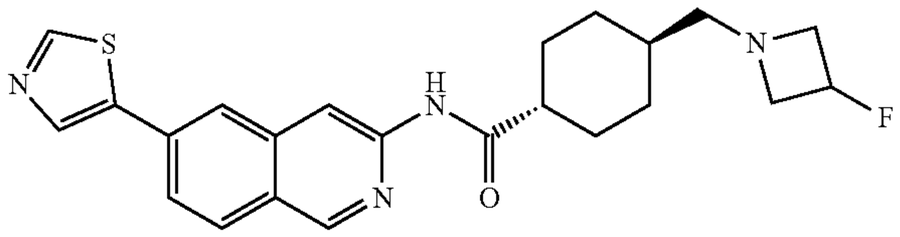
707



trans-4-(Dimethylamino)-N-(6-(thiazol-5-yl)isoquinolin-3-yl)cyclohexane-1-carboxamide 707

White solid (48.0 mg, 0.126 mmol, 25.1% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.12-1.22 (2H, m), 1.42-1.54 (2H, m), 1.83-1.97 (4H, m), 2.11-2.16 (1H, m), 2.18 (6H, s), 2.43-2.49 (1H, m), 7.85 (1H, dd, J=8.64, 1.51 Hz), 8.10 (1H, d, J=8.51 Hz), 8.19 (1H, s), 8.52 (1H, s), 8.55 (1H, s), 9.12 (1H, s), 9.19 (1H, s), 10.49 (1H, s); ESIMS found for $C_{21}H_{24}N_4OS$ m/z 381.2 (M+1).

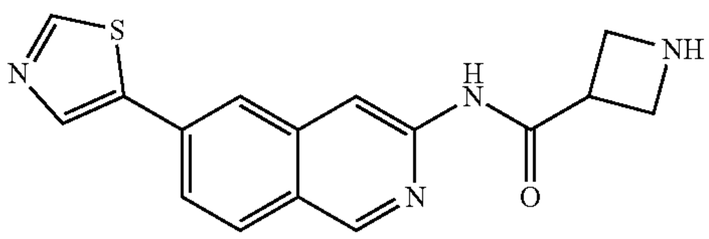
711



trans-4-((3-Fluoroazetidin-1-yl)methyl)-N-(6-(thiazol-5-yl)isoquinolin-3-yl)cyclohexane-1-carboxamide 711

Beige solid (22.0 mg, 0.052 mmol, 21.8% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 0.84-0.97 (2H, m), 1.21-1.33 (1H, m), 1.44 (2H, qd, J=12.76, 2.88 Hz), 1.80 (2H, br dd, J=12.76, 2.33 Hz), 1.86 (2H, br d, J=10.70 Hz), 2.29 (2H, d, J=6.86 Hz), 2.45-2.49 (1H, m), 2.97-3.08 (2H, m), 3.48-3.60 (2H, m), 5.12 (1H, dq, J=58.00, 5.20 Hz), 7.86 (1H, dd, J=8.51, 1.65 Hz), 8.10 (1H, d, J=8.51 Hz), 8.19 (1H, s), 8.52 (1H, s), 8.56 (1H, s), 9.12 (1H, s), 9.19 (1H, s), 10.49 (1H, s); ESIMS found for $C_{23}H_{25}FN_4OS$ m/z 425.2 (M+1).

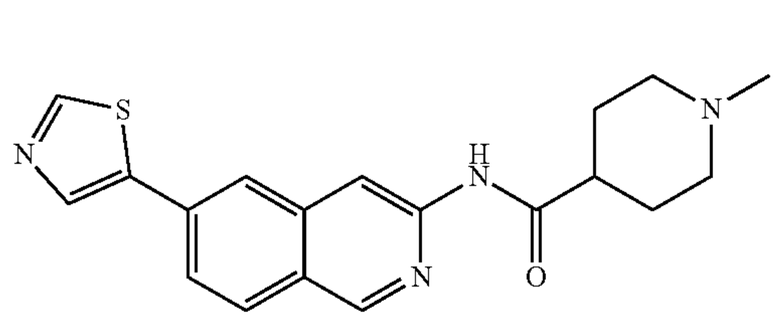
713



N-(6-(Thiazol-5-yl)isoquinolin-3-yl)azetidine-3-carboxamide 713

Orange solid (6.0 mg, 0.019 mmol, 8.4% yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 3.70 (2H, br t, J=7.96 Hz), 3.82 (1H, dt, J=15.09, 7.55 Hz), 3.87-3.93 (2H, m), 7.88 (1H, dd, J=8.51, 1.92 Hz), 8.11 (1H, d, J=8.51 Hz), 8.24 (1H, s), 8.57 (1H, br s), 8.57 (1H, s), 9.13 (1H, s), 9.20 (1H, s), 10.65 (1H, br s); ESIMS found for $C_{16}H_{14}N_4OS$ m/z 311.1 (M+1).

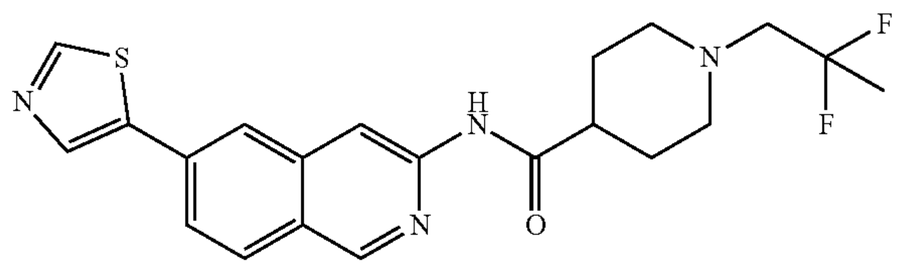
718



1-Methyl-N-(6-(thiazol-5-yl)isoquinolin-3-yl)piperidine-4-carboxamide 718

Beige solid (16.0 mg, 0.045 mmol, 21.1% yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.62-1.73 (2H, m), 1.74-1.81 (2H, m), 1.87 (2H, td, J=11.53, 1.92 Hz), 2.16 (3H, s), 2.51-2.56 (1H, m), 2.81 (2H, br d, J=11.25 Hz), 7.86 (1H, dd, J=8.64, 1.51 Hz), 8.10 (1H, d, J=8.51 Hz), 8.20 (1H, s), 8.53 (1H, s), 8.55 (1H, s), 9.12 (1H, s), 9.19 (1H, s), 10.54 (1H, s); ESIMS found for $C_{19}H_{20}N_4OS$ m/z 352.9 (M+1).

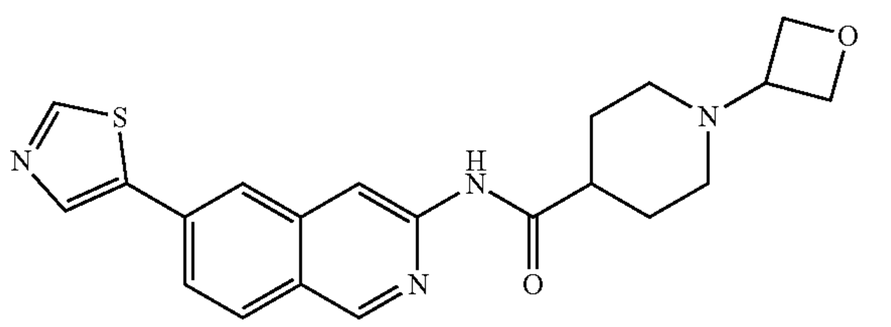
731



1-(2,2-Difluoropropyl)-N-(6-(thiazol-5-yl)isoquinolin-3-yl)piperidine-4-carboxamide 731

White solid (54.3 mg, 0.131 mmol, 52.2% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.63 (3H, t, J=19.07 Hz), 1.68-1.75 (2H, m), 1.75-1.81 (2H, m), 2.22 (2H, td, J=11.66, 2.47 Hz), 2.51-2.60 (1H, m), 2.71 (2H, t, J=14.00 Hz), 2.95 (2H, br d, J=11.53 Hz), 7.86 (1H, dd, J=8.64, 1.78 Hz), 8.10 (1H, d, J=8.78 Hz), 8.21 (1H, d, J=0.82 Hz), 8.53 (1H, s), 8.56 (1H, s), 9.13 (1H, s), 9.19 (1H, s), 10.56 (1H, s); ESIMS found for $C_{21}H_{22}F_2N_4OS$ m/z 417.2 (M+1).

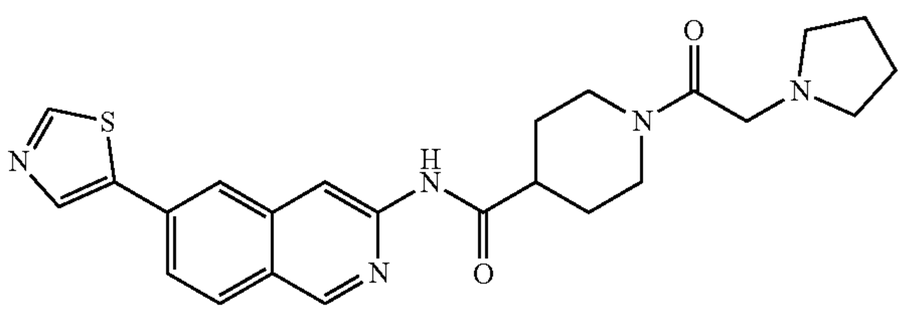
737



1-(Oxetan-3-yl)-N-(6-(thiazol-5-yl)isoquinolin-3-yl) piperidine-4-carboxamide 737

White solid (39.0 mg, 0.099 mmol, 42.9% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.64-1.73 (2H, m), 1.75-1.85 (4H, m), 2.53-2.61 (1H, m), 2.71-2.78 (2H, m), 3.35-3.41 (1H, m), 4.43 (2H, t, J=6.17 Hz), 4.53 (2H, t, J=6.45 Hz), 7.86 (1H, dd, J=8.51, 1.65 Hz), 8.10 (1H, d, J=8.51 Hz), 8.21 (1H, d, J=1.10 Hz), 8.55 (1H, s), 8.56 (1H, s), 9.12 (1H, s), 9.19 (1H, s), 10.56 (1H, s) ESIMS found for $C_{21}H_{22}N_4O_2S$ m/z 395.1 (M+1).

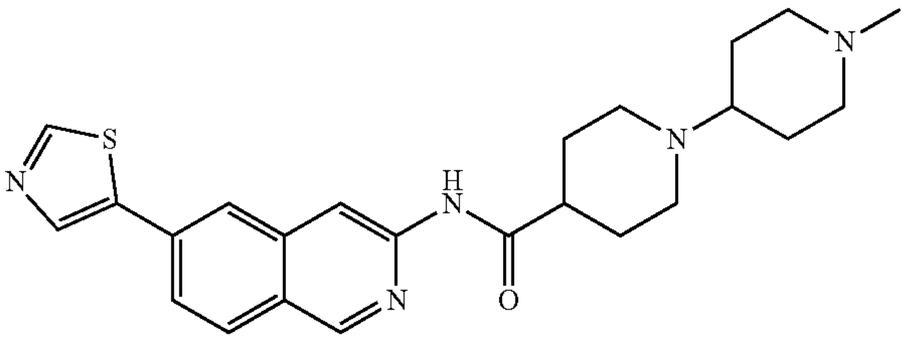
741



1-(2-(Pyrrolidin-1-yl)acetyl)-N-(6-(thiazol-5-yl)iso-quinolin-3-yl)piperidine-4-carboxamide 741

White solid (124.6 mg, 0.277 mmol, 69.7% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.42-1.55 (1H, m), 1.57-1.68 (1H, m), 1.72 (4H, br s), 1.85 (2H, br d, J=10.98 Hz), 2.55 (4H, br s), 2.58-2.67 (1H, m), 2.78-2.88 (1H, m), 3.03 (1H, br t, J=11.94 Hz), 3.25-3.30 (1H, m), 3.44 (1H, br d, J=13.17 Hz), 4.07 (1H, br d, J=14.00 Hz), 4.40 (1H, br d, J=12.62 Hz), 7.87 (1H, dd, J=8.51, 1.65 Hz), 8.11 (1H, d, J=8.78 Hz), 8.21 (1H, s), 8.53 (1H, s), 8.56 (1H, s), 9.13 (1H, s), 9.19 (1H, s), 10.64 (1H, s); ESIMS found for $C_{24}H_{27}N_5O_2S$ m/z 449.9 (M+1).

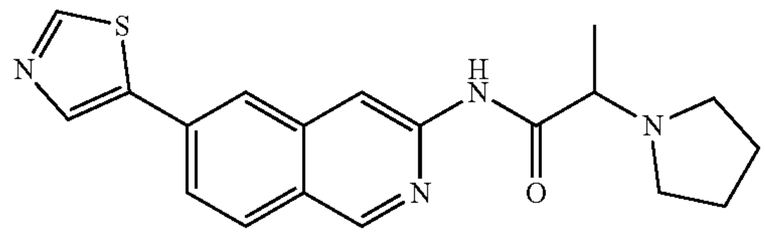
743



1'-Methyl-N-(6-(thiazol-5-yl)isoquinolin-3-yl)-[1,4'-bipiperidine]-4-carboxamide 743

Beige solid (55.0 mg, 0.126 mmol, 36.3% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.43 (2H, qd, J=11.94, 3.70 Hz), 1.58-1.71 (4H, m), 1.75-1.87 (4H, m), 2.09-2.20 (3H, m), 2.12 (3H, s), 2.51-2.57 (1H, m), 2.77 (2H, br d, J=11.53 Hz), 2.90 (2H, br d, J=11.25 Hz), 7.86 (1H, dd, J=8.51, 1.65 Hz), 8.10 (1H, d, J=8.51 Hz), 8.20 (1H, s), 8.54 (1H, s), 8.55 (1H, s), 9.12 (1H, s), 9.19 (1H, s), 10.52 (1H, s); ESIMS found for $C_{24}H_{29}N_5OS$ m/z 436.2 (M+1).

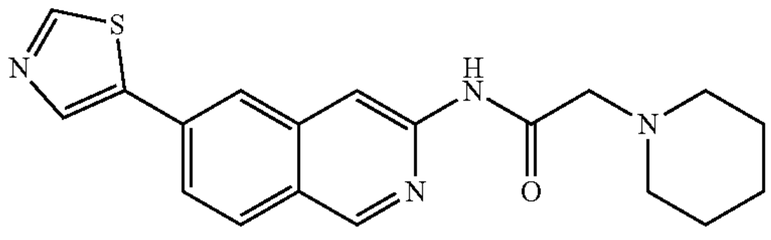
758



2-(Pyrrolidin-1-yl)-N-(6-(thiazol-5-yl)isoquinolin-3-yl)propanamide 758

Beige solid (40.0 mg, 0.114 mmol, 26.3% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.30 (3H, d, J=6.86 Hz), 1.74 (4H, br s), 2.56-2.68 (4H, m), 3.27-3.34 (1H, m), 7.88 (1H, dd, J=8.64, 1.78 Hz), 8.12 (1H, d, J=8.78 Hz), 8.25 (1H, d, J=0.82 Hz), 8.53 (1H, s), 8.57 (1H, s), 9.13 (1H, s), 9.20 (1H, s), 10.04 (1H, s); ESIMS found for $C_{19}H_{20}N_4OS$ m/z 353.2 (M+1).

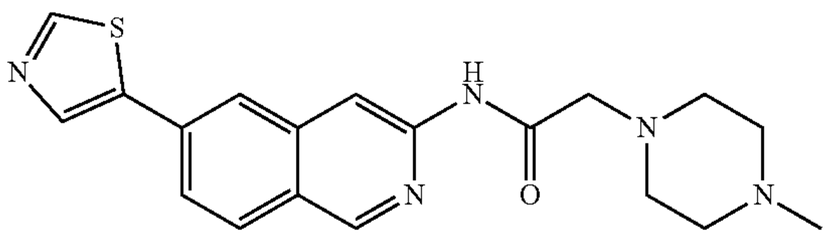
760



2-(Piperidin-1-yl)-N-(6-(thiazol-5-yl)isoquinolin-3-yl)acetamide 760

Yellow-white solid (8.0 mg, 0.023 mmol, 16.1% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.40-1.48 (2H, m), 1.59 (4H, dt, J=11.05, 5.59 Hz), 2.51-2.57 (4H, m), 3.18 (2H, s), 7.89 (1H, dd, J=8.51, 1.92 Hz), 8.13 (1H, d, J=8.51 Hz), 8.27 (1H, d, J=1.10 Hz), 8.53 (1H, s), 8.58 (1H, d, J=0.82 Hz), 9.14 (1H, s), 9.20 (1H, s), 9.99 (1H, s); ESIMS found for $C_{19}H_{20}N_4OS$ m/z 353.1 (M+1).

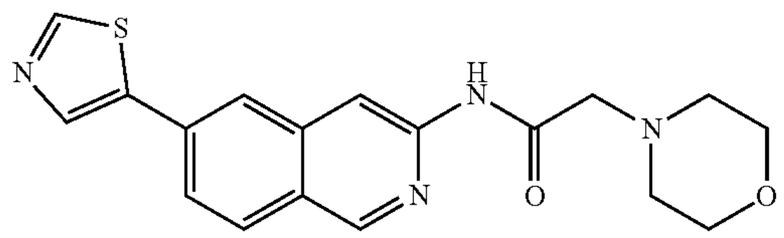
767



2-(4-Methylpiperazin-1-yl)-N-(6-(thiazol-5-yl)iso-quinolin-3-yl)acetamide 767

Beige solid (10.0 mg, 0.027 mmol, 8.2% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 2.19 (3H, s), 2.40 (4H, br s), 2.59 (4H, br s), 3.23 (2H, s), 7.89 (1H, dd, J=8.51, 1.65 Hz), 8.13 (1H, d, J=8.78 Hz), 8.28 (1H, s), 8.53 (1H, s), 8.58 (1H, s), 9.14 (1H, s), 9.20 (1H, s), 10.02 (1H, s); ESIMS found for $C_{19}H_{21}N_5OS$ m/z 368.0 (M+1).

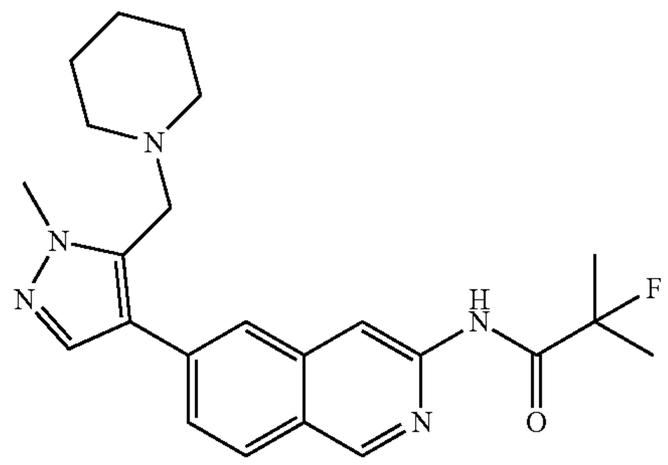
773



2-Morpholino-N-(6-(thiazol-5-yl)isoquinolin-3-yl) acetamide 773

Pale green solid (43.0 mg, 0.121 mmol, 42.5% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 2.54-2.62 (4H, m), 3.26 (2H, s), 3.62-3.69 (4H, m), 7.89 (1H, dd, J=8.64, 1.78 Hz), 8.13 (1H, d, J=8.51 Hz), 8.27 (1H, s), 8.53 (1H, s), 8.58 (1H, s), 9.15 (1H, s), 9.20 (1H, s), 10.10 (1H, s); ESIMS found for $C_{18}H_{18}N_4O_2S$ m/z 355.1 (M+1).

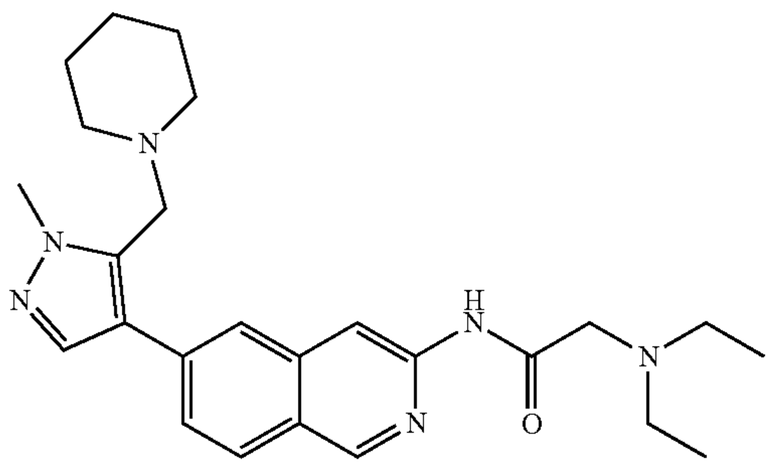
784



2-Fluoro-2-methyl-N-(6-(1-methyl-5-(piperidin-1-ylmethyl)-1H-pyrazol-4-yl)isoquinolin-3-yl)propanamide 784

Beige solid (40.0 mg, 0.098 mmol, 36.9% yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.38 (2H, br d, J=3.29 Hz), 1.49 (4H, quin, J=5.21 Hz), 1.64 (6H, d, J=22.00 Hz), 2.37 (4H, br s), 3.65 (2H, s), 3.92 (3H, s), 7.76 (1H, dd, J=8.51, 1.65 Hz), 7.82 (1H, s), 8.08 (1H, d, J=8.51 Hz), 8.13 (1H, s), 8.42 (1H, s), 9.13 (1H, s), 9.85 (1H, d, J=3.84 Hz); ESIMS found for $C_{23}H_{28}FN_5O$ m/z 410.2 (M+1).

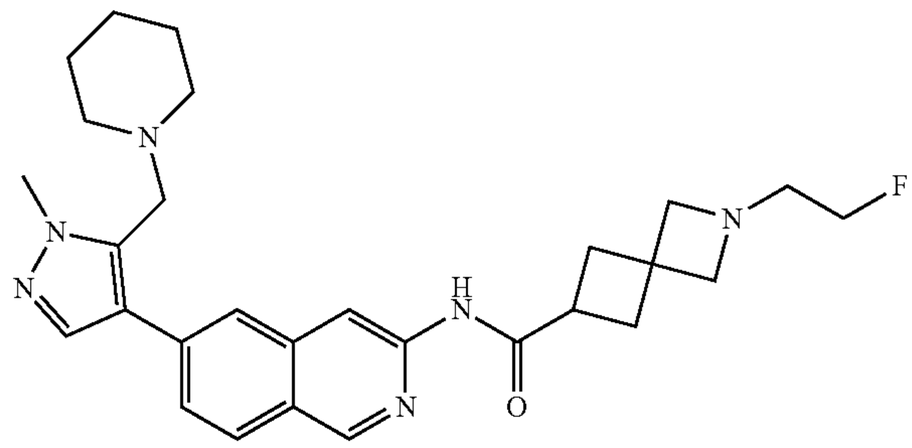
785



2-(Diethylamino)-N-(6-(1-methyl-5-(piperidin-1-ylmethyl)-1H-pyrazol-4-yl) isoquinolin-3-yl)acetamide 785

Orange gum (200.0 mg, 0.460 mmol, 60.1% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.05 (6H, t, J=7.14 Hz), 1.34-1.42 (2H, m), 1.44-1.54 (4H, m), 2.36 (4H, br s), 2.64 (4H, q, J=6.95 Hz), 3.24 (2H, s), 3.64 (2H, s), 3.91 (3H, s), 7.72 (1H, dd, J=8.37, 1.51 Hz), 7.81 (1H, s), 8.04 (1H, d, J=8.51 Hz), 8.12 (1H, s), 8.45 (1H, s), 9.08 (1H, s), 9.93 (1H, s); ESIMS found for $C_{25}H_{34}N_6O$ m/z 435.3 (M+1).

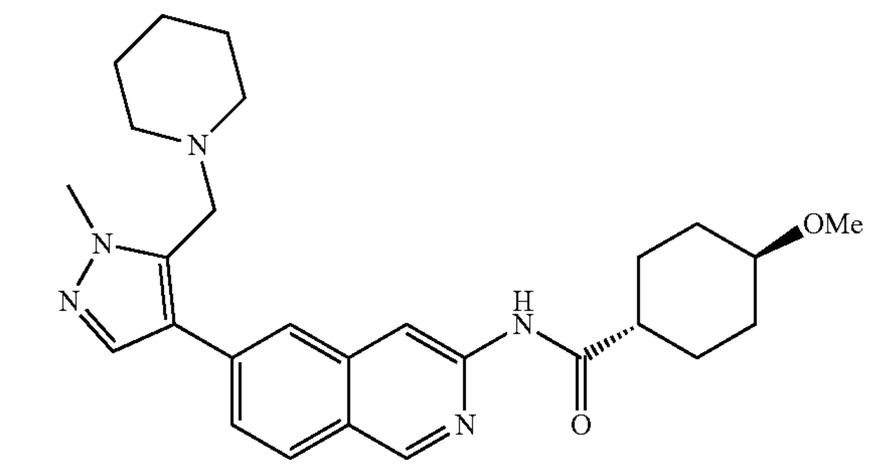
791



2-(2-Fluoroethyl)-N-(6-(1-methyl-5-(piperidin-1-ylmethyl)-1H-pyrazol-4-yl) isoquinolin-3-yl)-2-azaspiro[3.3]heptane-6-carboxamide 791

White solid (20.0 mg, 0.041 mmol, 23.2% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.38 (2H, br d, J=3.57 Hz), 1.45-1.54 (4H, m), 2.24-2.33 (4H, m), 2.36 (4H, br s), 2.60 (2H, dt, J=28.60, 4.95 Hz), 3.12 (2H, s), 3.22 (2H, s), 3.27 (1H, t, J=8.37 Hz), 3.65 (2H, s), 3.91 (3H, s), 4.36 (2H, dt, J=47.80, 4.95 Hz), 7.69 (1H, dd, J=8.51, 1.37 Hz), 7.80 (1H, s), 8.02 (1H, d, J=8.51 Hz), 8.04 (1H, s), 8.46 (1H, s), 9.06 (1H, s), 10.39 (1H, s); ESIMS found for $C_{28}H_{35}FN_6O$ m/z 491.3 (M+1).

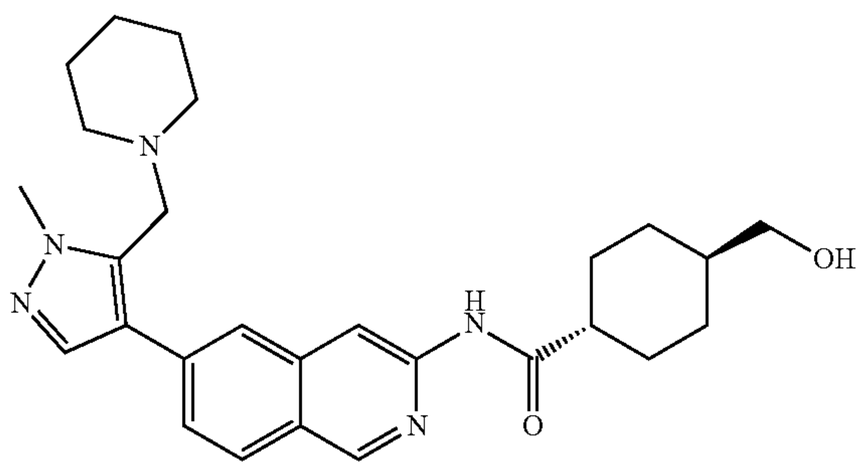
795



trans-4-Methoxy-N-(6-(1-methyl-5-(piperidin-1-ylmethyl)-1H-pyrazol-4-yl)isoquinolin-3-yl)cyclohexane-1-carboxamide 795

White solid (33.7 mg, 0.073 mmol, 54.7% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.07-1.18 (2H, m), 1.38 (2H, br d, J=3.29 Hz), 1.43-1.52 (6H, m), 1.89 (2H, br d, J=11.53 Hz), 2.04-2.12 (2H, m), 2.36 (4H, br s), 2.51-2.57 (1H, m), 3.12 (1H, tt, J=10.67, 4.15 Hz), 3.25 (3H, s), 3.64 (2H, s), 3.91 (3H, s), 7.69 (1H, dd, J=8.37, 1.51 Hz), 7.80 (1H, s), 8.02 (1H, d, J=8.51 Hz), 8.04 (1H, br s), 8.45 (1H, s), 9.07 (1H, s), 10.46 (1H, s); ESIMS found for $C_{27}H_{35}N_5O_2$ m/z 462.3 (M+1).

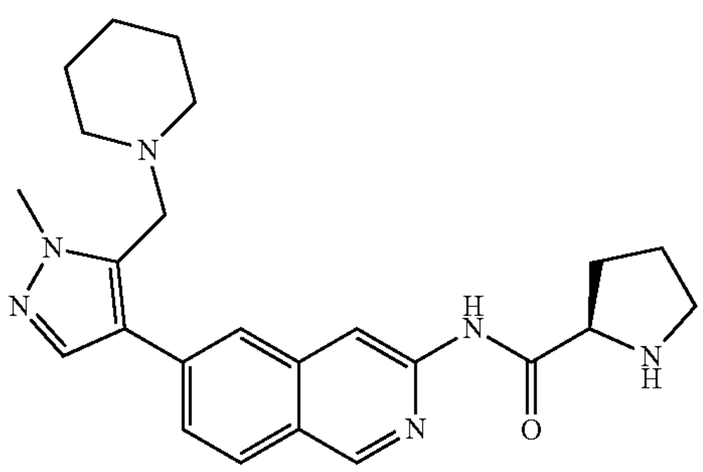
798



trans-4-(Hydroxymethyl)-N-(6-(1-methyl-5-(piperidin-1-ylmethyl)-1H-pyrazol-4-yl)isoquinolin-3-yl) cyclohexane-1-carboxamide 798

White solid (50.6 mg, 0.110 mmol, 103% yield). ^{11}H NMR (499 MHz, DMSO-d_6) δ ppm 0.90-1.01 (2H, m), 1.32-1.42 (4H, m), 1.42-1.53 (6H, m), 1.80 (2H, br dd, J=13.04, 2.61 Hz), 1.85-1.91 (2H, m), 2.36 (4H, br s), 3.24 (2H, t, J=5.63 Hz), 3.64 (2H, s), 3.91 (3H, s), 4.39 (1H, t, J=5.21 Hz), 7.68 (1H, dd, J=8.37, 1.51 Hz), 7.80 (1H, s), 8.00-8.06 (2H, m), 8.46 (1H, s), 9.07 (1H, s), 10.42 (1H, s); ESIMS found for $C_{27}H_{35}N_5O_2$ m/z 462.3 (M+1).

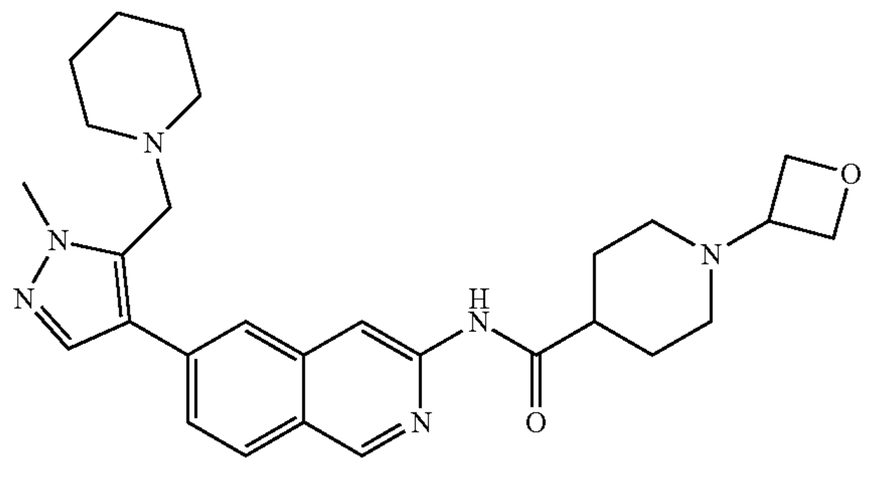
803



(R)—N-(6-(1-Methyl-5-(piperidin-1-ylmethyl)-1H-pyrazol-4-yl)isoquinolin-3-yl)pyrrolidine-2-carboxamide 803

Off-white solid (40.0 mg, 0.096 mmol, 58.7% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.38 (2H, br s), 1.46-1.52 (4H, m), 1.67 (2H, quin, J=6.79 Hz), 1.80-1.89 (1H, m), 2.05-2.15 (1H, m), 2.36 (4H, br s), 2.87 (1H, dt, J=10.15, 6.31 Hz), 2.97 (1H, dt, J=10.15, 6.72 Hz), 3.64 (2H, s), 3.80 (1H, dd, J=9.06, 5.49 Hz), 3.91 (3H, s), 7.71 (1H, dd, J=8.51, 1.65 Hz), 7.81 (1H, s), 8.04 (1H, d, J=8.51 Hz), 8.10 (1H, s), 8.46 (1H, s), 9.07 (1H, s), 10.36 (1H, s); ESIMS found for $C_{24}H_{30}N_6O$ m/z 419.3 (M+1).

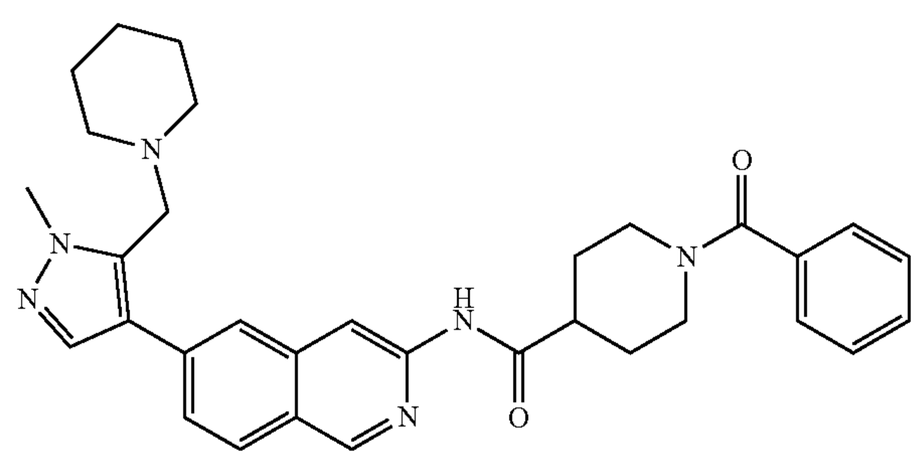
826



N-(6-(1-Methyl-5-(piperidin-1-ylmethyl)-1H-pyrazol-4-yl)isoquinolin-3-yl)-1-(oxetan-3-yl)piperidine-4-carboxamide 826

Off-white solid (40.0 mg, 0.082 mmol, 27.2% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.34-1.42 (2H, m), 1.44-1.53 (4H, m), 1.63-1.73 (2H, m), 1.74-1.86 (4H, m), 2.36 (4H, br s), 2.53-2.61 (1H, m), 2.71-2.82 (2H, m), 3.40 (1H, br s), 3.65 (2H, br s), 3.91 (3H, s), 4.44 (2H, br t, J=5.90 Hz), 4.50-4.57 (2H, m), 7.69 (1H, dd, J=8.64, 1.51 Hz), 7.79 (1H, s), 7.99-8.06 (2H, m), 8.47 (1H, s), 9.07 (1H, s), 10.48 (1H, s); ESIMS found for $C_{28}H_{36}N_6O_2$ m/z 489.3 (M+1).

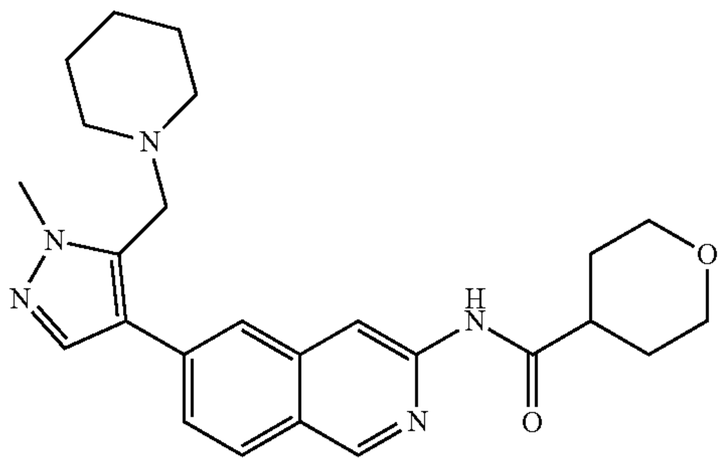
831



1-Benzoyl-N-(6-(1-methyl-5-(piperidin-1-ylmethyl)-1H-pyrazol-4-yl) isoquinolin-3-yl)piperidine-4-carboxamide 831

White solid (53.0 mg, 0.099 mmol, 58.6% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.38 (2H, br d, J=3.02 Hz), 1.45-1.54 (4H, m), 1.57-1.71 (2H, m), 1.74-1.86 (1H, m), 1.89-1.98 (1H, m), 2.36 (4H, br s), 2.45-2.49 (1H, m), 2.86 (2H, ddt, J=11.25, 7.55, 3.77, 3.77 Hz), 3.02-3.16 (1H, m), 3.65 (2H, s), 3.91 (3H, s), 4.46-4.61 (1H, m), 7.37-7.43 (2H, m), 7.43-7.49 (3H, m), 7.70 (1H, dd, J=8.51, 1.37 Hz), 7.80 (1H, s), 8.03 (1H, d, J=8.51 Hz), 8.06 (1H, s), 8.46 (1H, s), 9.08 (1H, s), 10.58 (1H, s); ESIMS found for $C_{32}H_{36}N_6O_2$ m/z 537.3 (M+1).

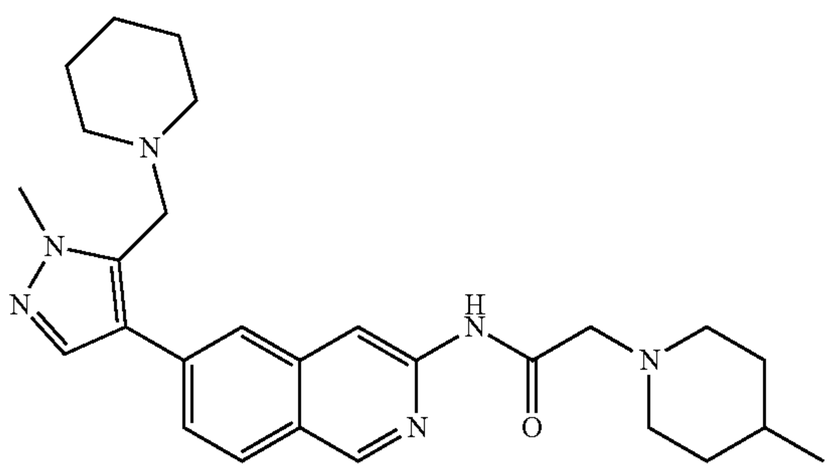
839



N-(6-(1-Methyl-5-(piperidin-1-ylmethyl)-1H-pyrazol-4-yl)isoquinolin-3-yl) tetrahydro-2H-pyran-4-carboxamide 839

White amorphous solid (25.8 mg, 0.060 mmol, 69.3% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.35-1.41 (2H, m), 1.46-1.52 (4H, m), 1.66-1.77 (4H, m), 2.36 (4H, br d, J=1.65 Hz), 2.77-2.88 (1H, m), 3.33-3.39 (2H, m), 3.65 (2H, s), 3.89-3.94 (2H, m), 3.91 (3H, s), 7.66-7.73 (1H, m), 7.80 (1H, s), 8.00-8.06 (2H, m), 8.46 (1H, s), 9.08 (1H, s), 10.52 (1H, s); ESIMS found for $C_{25}H_{31}N_5O_2$ m/z 434.2 (M+1).

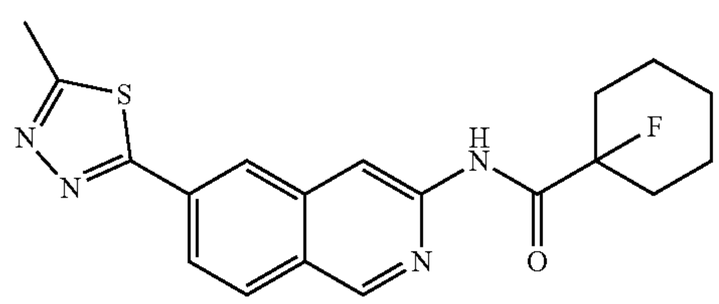
851



N-(6-(1-Methyl-5-(piperidin-1-ylmethyl)-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(4-methylpiperidin-1-yl) acetamide 851

Off-white solid (180.0 mg, 0.391 mmol, 54.6% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 0.93 (3H, d, J=6.31 Hz), 1.20-1.30 (2H, m), 1.33-1.42 (3H, m), 1.44-1.53 (4H, m), 1.63 (2H, br d, J=11.53 Hz), 2.16-2.24 (2H, m), 2.36 (4H, br s), 2.87 (2H, br d, J=11.53 Hz), 3.18 (2H, s), 3.65 (2H, s), 3.91 (3H, s), 7.72 (1H, dd, J=8.51, 1.37 Hz), 7.82 (1H, s), 8.05 (1H, d, J=8.78 Hz), 8.12 (1H, s), 8.45 (1H, s), 9.08 (1H, s), 9.91 (1H, s); ESIMS found for $C_{27}H_{36}N_6O$ m/z 461.3 (M+1).

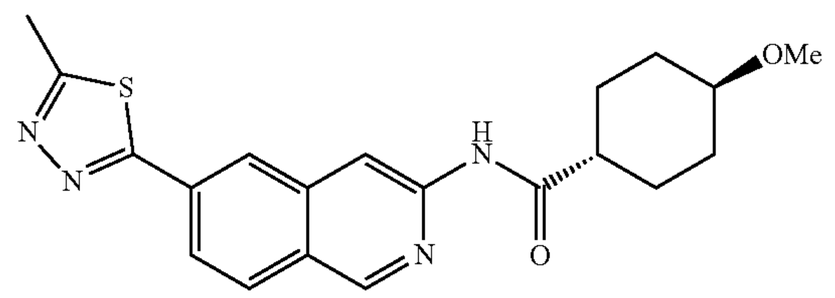
883



1-Fluoro-N-(6-(5-methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)cyclohexane-1-carboxamide 883

Off-white solid (36.5 mg, 0.099 mmol, 63.5% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.31-1.40 (1H, m), 1.51-1.62 (2H, m), 1.69 (3H, br d, J=9.33 Hz), 1.87-2.02 (4H, m), 2.83 (3H, s), 8.15 (1H, dd, J=8.51, 1.65 Hz), 8.24 (1H, d, J=8.51 Hz), 8.53 (1H, s), 8.58 (1H, s), 9.27 (1H, s), 9.97 (1H, d, J=3.84 Hz); ESIMS found for $C_{19}H_{19}FN_4OS$ m/z 371.1 (M+1).

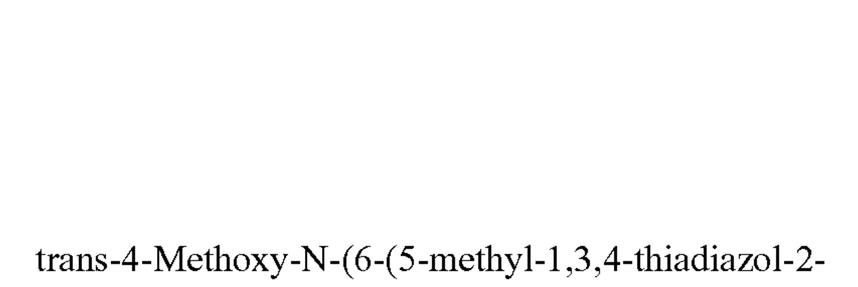
885



trans-4-Methoxy-N-(6-(5-methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl) cyclohexane-1-carboxamide 885

White solid (33.4 mg, 0.087 mmol, 21.2% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.08-1.19 (2H, m), 1.44-1.56 (2H, m), 1.88-1.94 (2H, m), 2.05-2.13 (2H, m), 2.52-2.58 (1H, m), 2.83 (3H, s), 3.09-3.17 (1H, m), 3.25 (3H, s), 8.09 (1H, dd, J=8.65, 1.51 Hz), 8.19 (1H, d, J=8.51 Hz), 8.44 (1H, s), 8.60 (1H, s), 9.21 (1H, s), 10.60 (1H, s); ESIMS found for $C_{20}H_{22}N_4O_2S$ m/z 383.15 (M+1).

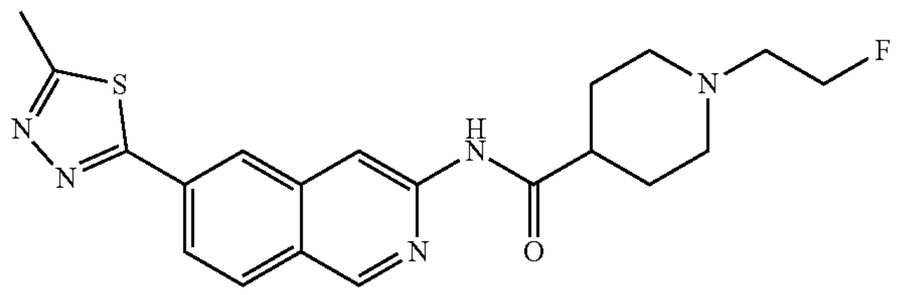
888



trans-4-(Hydroxymethyl)-N-(6-(5-methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)cyclohexane-1-carboxamide 888

White solid (12.4 mg, 0.032 mmol, 39.0% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 0.90-1.02 (2H, m), 1.30-1.40 (1H, m), 1.46 (2H, qd, J=12.76, 3.43 Hz), 1.81 (2H, br dd, J=13.04, 2.61 Hz), 1.86-1.93 (2H, m), 2.52-2.56 (1H, m), 2.83 (3H, s), 3.24 (2H, t, J=5.76 Hz), 4.39 (1H, t, J=5.35 Hz), 8.08 (1H, dd, J=8.51, 1.65 Hz), 8.19 (1H, d, J=8.51 Hz), 8.43 (1H, s), 8.61 (1H, s), 9.21 (1H, s), 10.57 (1H, s); ESIMS found for $C_{20}H_{22}N_4O_2S$ m/z 383.1 (M+1).

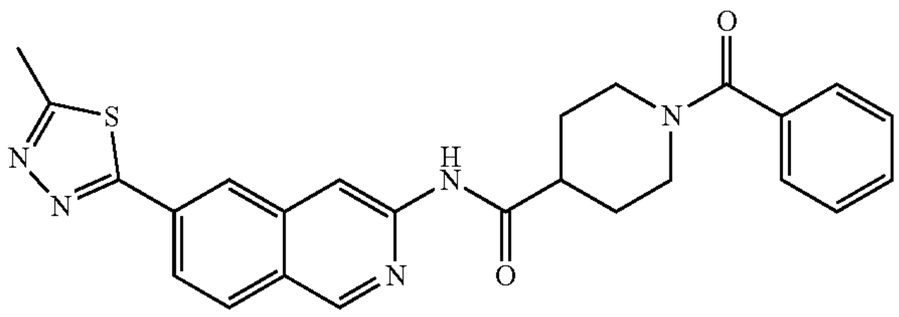
900



1-(2-Fluoroethyl)-N-(6-(5-methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl) piperidine-4-carboxamide 900

Beige solid (41.0 mg, 0.103 mmol, 19.5% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.69 (2H, qd, J=12.12, 3.70 Hz), 1.76-1.85 (2H, m), 2.02-2.09 (2H, m), 2.52-2.57 (1H, m), 2.62 (2H, dt, J=28.35, 4.95 Hz), 2.83 (3H, s), 2.95 (2H, br d, J=11.53 Hz), 4.54 (2H, dt, J=47.80, 4.95 Hz), 8.09 (1H, dd, J=8.51, 1.65 Hz), 8.19 (1H, d, J=8.51 Hz), 8.44 (1H, s), 8.63 (1H, s), 9.21 (1H, s), 10.62 (1H, s); ESIMS found for $C_{20}H_{22}FN_5OS$ m/z 400.15 (M+1).

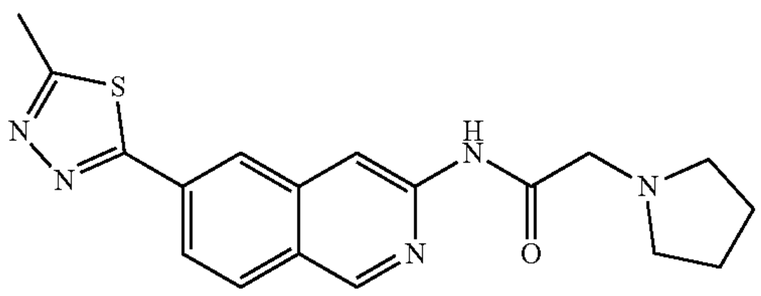
921



1-Benzoyl-N-(6-(5-methyl-1,3,4-thiadiazol-2-yl) isoquinolin-3-yl)piperidine-4-carboxamide 921

Off-white solid (78.5 mg, 0.172 mmol, 42.8% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.64 (2H, br s), 1.77-1.89 (1H, m), 1.90-2.04 (1H, m), 2.78-2.92 (2H, m), 2.83 (3H, s), 3.10 (1H, tdd, J=5.01, 5.01, 2.88, 1.37 Hz), 3.58-3.76 (1H, m), 4.42-4.61 (1H, m), 7.37-7.43 (2H, m), 7.43-7.49 (3H, m), 8.10 (1H, dd, J=8.51, 1.65 Hz), 8.19 (1H, d, J=8.51 Hz), 8.46 (1H, d, J=0.82 Hz), 8.62 (1H, s), 9.22 (1H, s), 10.72 (1H, s); ESIMS found for $C_{25}H_{23}N_5O_2S$ m/z 458.2 (M+1).

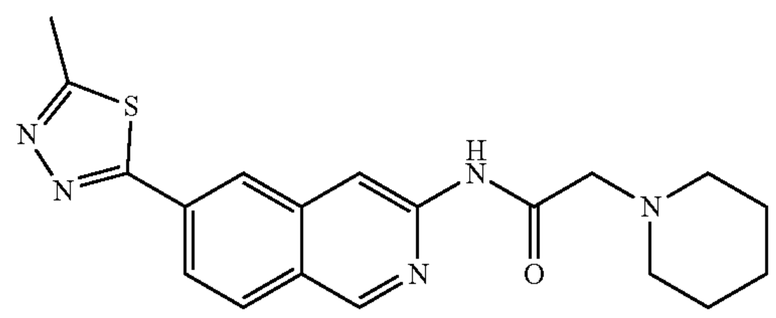
932



N-(6-(5-Methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)-2-(pyrrolidin-1-yl) acetamide 932

Beige solid (46.0 mg, 0.130 mmol, 21.7% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.78 (7H, dt, J=6.86, 3.16 Hz), 2.62-2.70 (4H, m), 2.83 (3H, s), 3.38 (2H, s), 8.12 (1H, dd, J=8.51, 1.65 Hz), 8.21 (1H, d, J=8.51 Hz), 8.50 (1H, s), 8.61 (1H, s), 9.22 (1H, s), 10.08 (1H, s); ESIMS found for $C_{18}H_{19}N_5OS$ m/z 354.1 (M+1).

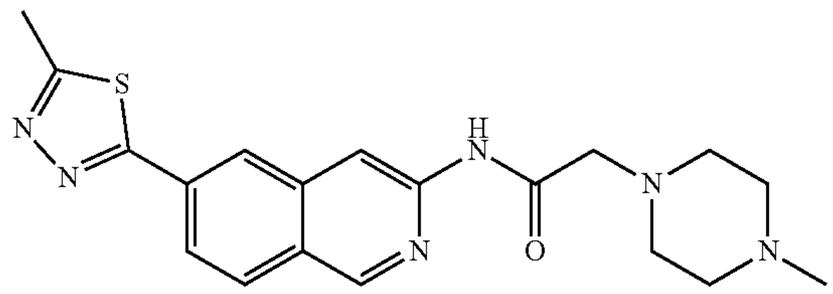
939



N-(6-(5-Methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)-2-(piperidin-1-yl) acetamide 939

Beige solid (77.0 mg, 0.210 mmol, 21.0% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.39-1.47 (2H, m), 1.59 (4H, quin, J=5.56 Hz), 2.52-2.57 (4H, m), 2.83 (3H, s), 3.19 (2H, s), 8.12 (1H, dd, J=8.51, 1.65 Hz), 8.21 (1H, d, J=8.51 Hz), 8.51 (1H, s), 8.61 (1H, s), 9.22 (1H, s), 10.06 (1H, s); ESIMS found for $C_{19}H_{21}N_5OS$ m/z 368.2 (M+1).

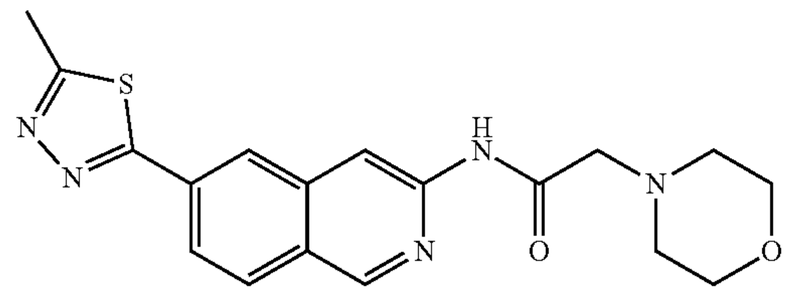
946



N-(6-(5-Methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)-2-(4-methylpiperazin-1-yl)acetamide 946

Beige solid (11.0 mg, 0.029 mmol, 8.7% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 2.19 (3H, s), 2.40 (4H, br s), 2.59 (4H, br s), 2.83 (3H, s), 3.24 (2H, s), 8.12 (1H, dd, J=8.78, 1.65 Hz), 8.21 (1H, d, J=8.51 Hz), 8.51 (1H, s), 8.61 (1H, s), 9.23 (1H, s), 10.09 (1H, s); ESIMS found for $C_{19}H_{22}N_6OS$ m/z 383.2 (M+1).

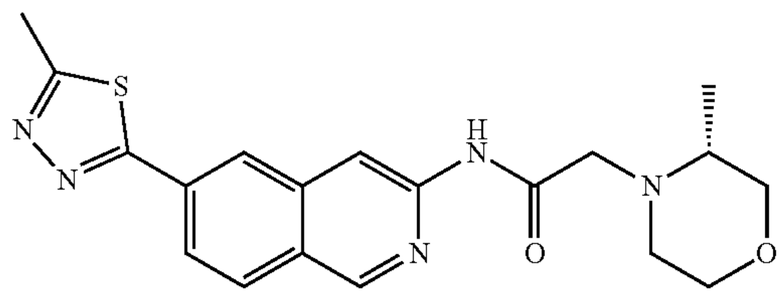
952



N-(6-(5-Methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)-2-morpholinoacetamide 952

Pale yellow solid (11.0 mg, 0.030 mmol, 9.6% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 2.55-2.61 (4H, m), 2.83 (3H, s), 3.27 (2H, s), 3.62-3.70 (4H, m), 8.12 (1H, dd, J=8.51, 1.65 Hz), 8.21 (1H, d, J=8.78 Hz), 8.51 (1H, s), 8.62 (1H, s), 9.23 (1H, s), 10.17 (1H, s); ESIMS found for $C_{18}H_{19}N_5O_2S$ m/z 370.1 (M+1).

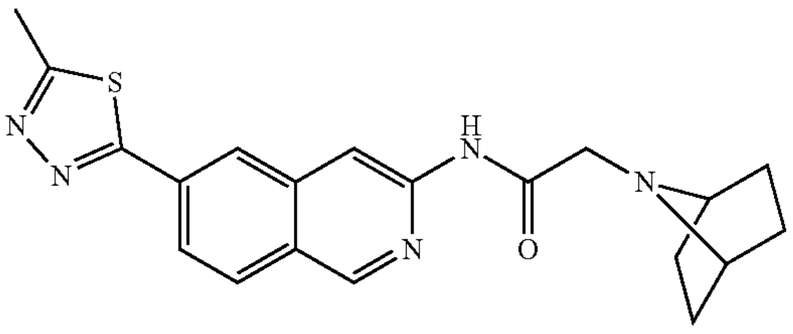
953



(R)—N-(6-(5-Methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)-2-(3-methylmorpholino)acetamide 953

Beige solid (66.0 mg, 0.172 mmol, 23.1% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 0.96 (3H, d, J=6.31 Hz), 2.54-2.60 (1H, m), 2.63 (1H, ddd, J=9.06, 6.17, 2.88 Hz), 2.80-2.82 (1H, m), 2.83 (3H, s), 3.19 (1H, dd, J=11.11, 8.92 Hz), 3.21 (1H, d, J=16.47 Hz), 3.49 (1H, d, J=16.47 Hz), 3.54-3.62 (1H, m), 3.68 (1H, dd, J=11.25, 3.02 Hz), 3.71-3.79 (1H, m), 8.08-8.18 (1H, m), 8.22 (1H, d, J=8.51 Hz), 8.51 (1H, s), 8.62 (1H, s), 9.23 (1H, s), 10.13 (1H, s); ESIMS found for $C_{19}H_{21}N_5O_2S$ m/z 384.2 (M+1).

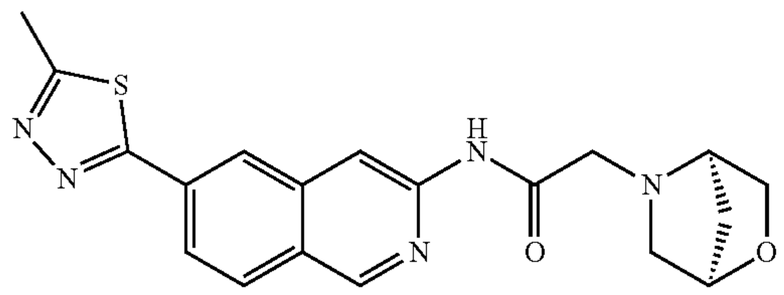
959



2-(7-Azabicyclo[2.2.1]heptan-7-yl)-N-(6-(5-methyl-1,3,4-thiadiazol-2-yl) isoquinolin-3-yl)acetamide 959

Beige solid (27.0 mg, 0.071 mmol, 18.7% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.34 (4H, d, J=7.14 Hz), 1.71-1.79 (4H, m), 2.83 (3H, s), 3.21 (2H, s), 3.35-3.40 (2H, m), 8.12 (1H, dd, J=8.51, 1.65 Hz), 8.22 (1H, d, J=8.51 Hz), 8.52 (1H, s), 8.63 (1H, s), 9.22 (1H, s), 10.21 (1H, s); ESIMS found for $C_{20}H_{21}N_5OS$ m/z 380.1 (M+1).

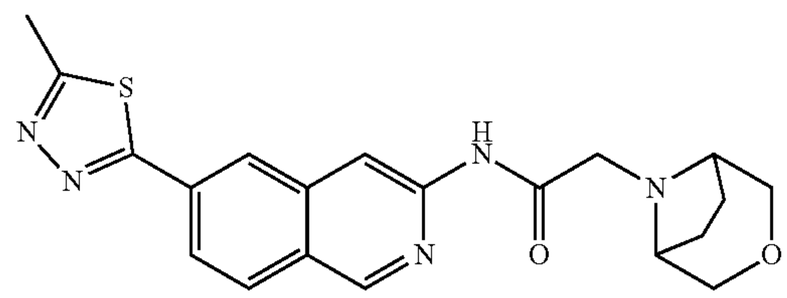
960



2-((1R,4R)-2-Oxa-5-azabicyclo[2.2.1]heptan-5-yl)-N-(6-(5-methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)acetamide 960

Off-white solid (110.0 mg, 0.288 mmol, 47.5% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.67 (1H, dd, J=9.74, 0.96 Hz), 1.87 (1H, dd, J=9.74, 1.78 Hz), 2.63 (1H, d, J=9.88 Hz), 2.83 (3H, s), 2.96 (1H, dd, J=9.88, 1.65 Hz), 3.48 (2H, d, J=4.94 Hz), 3.59 (1H, dd, J=7.68, 1.65 Hz), 3.64 (1H, s), 3.88 (1H, d, J=7.41 Hz), 4.41 (1H, s), 8.12 (1H, dd, J=8.51, 1.65 Hz), 8.22 (1H, d, J=8.78 Hz), 8.51 (1H, s), 8.62 (1H, s), 9.23 (1H, s), 10.07 (1H, s); ESIMS found for $C_{19}H_{19}N_5O_2S$ m/z 382.1 (M+1).

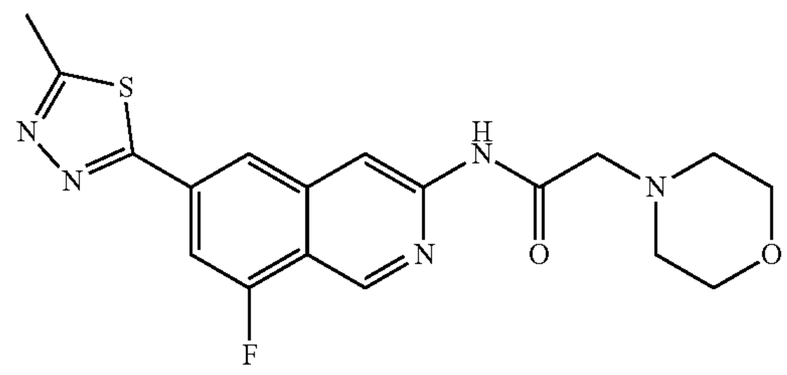
962



2-(3-Oxa-8-azabicyclo[3.2.1]octan-8-yl)-N-(6-(5-methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)acetamide 962

Off-white solid (175.0 mg, 0.065 mmol, 17.4% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.76-1.82 (2H, m), 1.87-1.94 (2H, m), 2.83 (3H, s), 3.16 (2H, s), 3.18 (2H, br d, J=1.10 Hz), 3.52 (2H, dd, J=10.57, 1.51 Hz), 3.68 (2H, d, J=10.43 Hz), 8.13 (1H, dd, J=8.51, 1.65 Hz), 8.22 (1H, d, J=8.78 Hz), 8.52 (1H, s), 8.63 (1H, s), 9.25 (1H, s), 10.28 (1H, s); ESIMS found for $C_{20}H_{21}N_5O_2S$ m/z 396.15 (M+1).

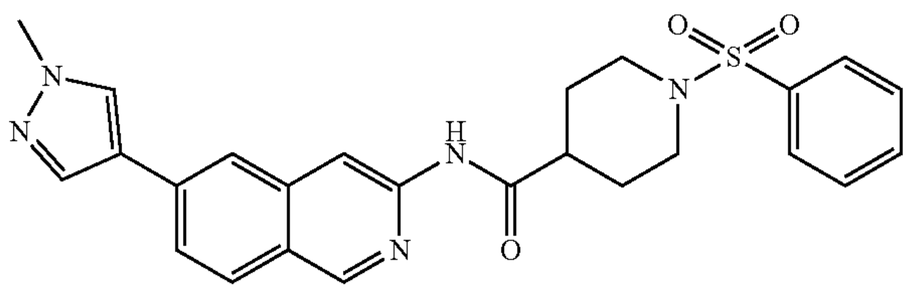
963



N-(8-Fluoro-6-(5-methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)-2-morpholinoacetamide 963

Beige solid (25.0 mg, 0.065 mmol, 17.4% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 2.55-2.63 (4H, m), 2.83 (3H, s), 3.28 (2H, s), 3.61-3.69 (4H, m), 7.89 (1H, dd, J=11.11, 1.24 Hz), 8.40 (1H, s), 8.68 (1H, s), 9.34 (1H, s), 10.32 (1H, s); ESIMS found for $C_{18}H_{18}FN_5O_2S$ m/z 388.1 (M+1).

964

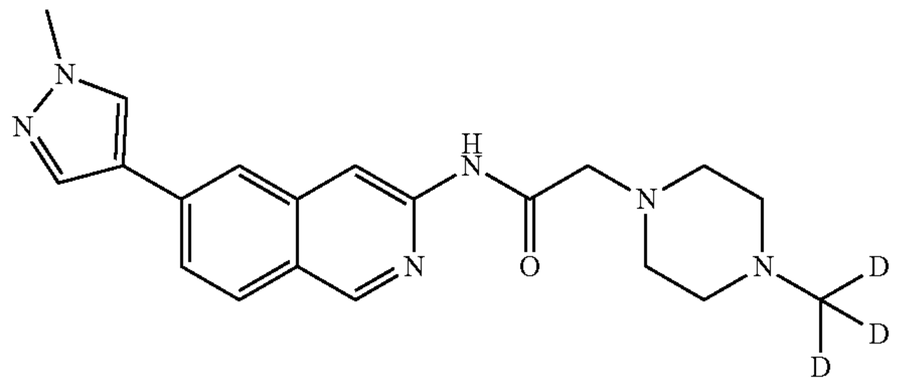


N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-1-(phenylsulfonyl) piperidine-4-carboxamide 964

White solid (81.0 mg, 0.170 mmol, 63.7% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.62-1.75 (2H, m), 1.90

(2H, br dd, J=13.58, 2.88 Hz), 2.27-2.36 (2H, m), 2.51-2.56 (1H, m), 3.69 (2H, br d, J=12.08 Hz), 3.90 (3H, s), 7.65-7.70 (2H, m), 7.72-7.80 (4H, m), 7.99 (1H, d, J=8.51 Hz), 8.03 (1H, s), 8.07 (1H, s), 8.34 (1H, s), 8.39 (1H, s), 9.01 (1H, s), 10.45 (1H, s); ESIMS found for $C_{25}H_{25}N_5O_3S$ m/z 475.9 (M+1).

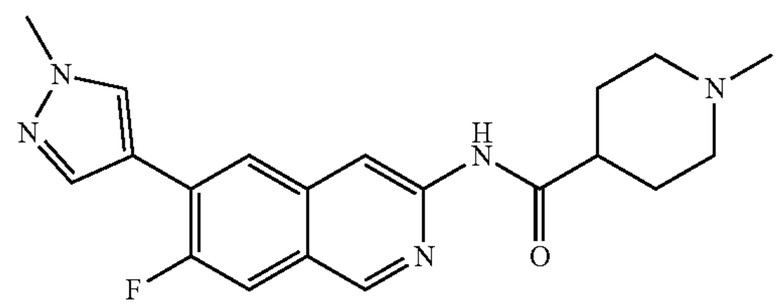
965



N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(4-(methyl-d3) piperazin-1-yl)acetamide 965

Beige solid (70.0 mg, 0.191 mmol, 28.9% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 2.40 (4H, br s), 2.58 (4H, br s), 3.22 (2H, s), 3.90 (3H, s), 7.77 (1H, dd, J=8.51, 1.65 Hz), 8.02 (1H, d, J=8.51 Hz), 8.10 (2H, s), 8.37 (1H, s), 8.43 (1H, s), 9.04 (1H, s), 9.92 (1H, s); ESIMS found for $C_{20}H_{21}[^2H_3]N_6O$ m/z 368.2 (M+1).

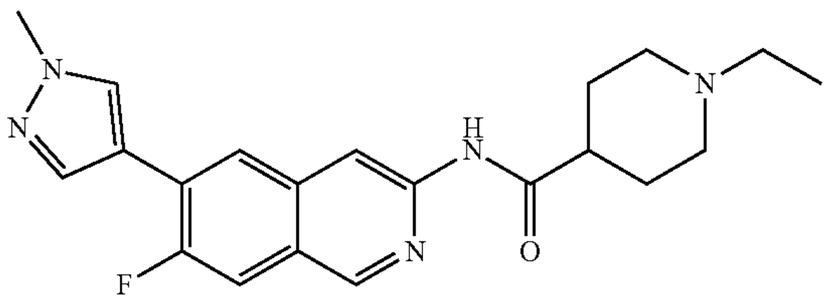
966



N-(7-Fluoro-6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-1-methylpiperidine-4-carboxamide 966

White solid (65.0 mg, 0.177 mmol, 80.2% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.62-1.72 (2H, m), 1.73-1.80 (2H, m), 1.86 (2H, td, J=11.66, 2.20 Hz), 2.16 (3H, s), 2.45-2.55 (1H, m), 2.76-2.85 (2H, m), 3.93 (3H, s), 7.89 (1H, d, J=11.80 Hz), 8.10 (1H, s), 8.26 (1H, d, J=7.41 Hz), 8.30 (1H, d, J=2.74 Hz), 8.49 (1H, s), 9.03 (1H, s), 10.49 (1H, s); ESIMS found for $C_{20}H_{22}FN_5O$ m/z 368.2 (M+1).

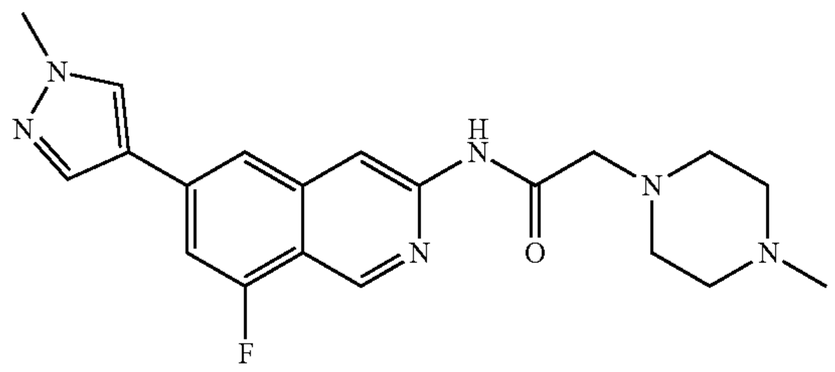
967



1-Ethyl-N-(7-fluoro-6-(1-methyl-1H-pyrazol-4-yl) isoquinolin-3-yl) piperidine-4-carboxamide 967

White solid (20.0 mg, 0.052 mmol, 26.9% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.00 (3H, t, J=7.14 Hz), 1.67 (2H, td, J=12.21, 3.57 Hz), 1.75-1.81 (2H, m), 1.86 (2H, td, J=11.73, 2.06 Hz), 2.31 (2H, q, J=7.14 Hz), 2.51-2.58 (1H, m), 2.87-2.95 (2H, m), 3.93 (3H, s), 7.89 (1H, d, J=11.53 Hz), 8.10 (1H, d, J=0.82 Hz), 8.26 (1H, d, J=7.41 Hz), 8.30 (1H, d, J=2.47 Hz), 8.50 (1H, s), 9.03 (1H, s), 10.49 (1H, s); ESIMS found for $C_{21}H_{24}FN_5O$ m/z 382.2 (M+1).

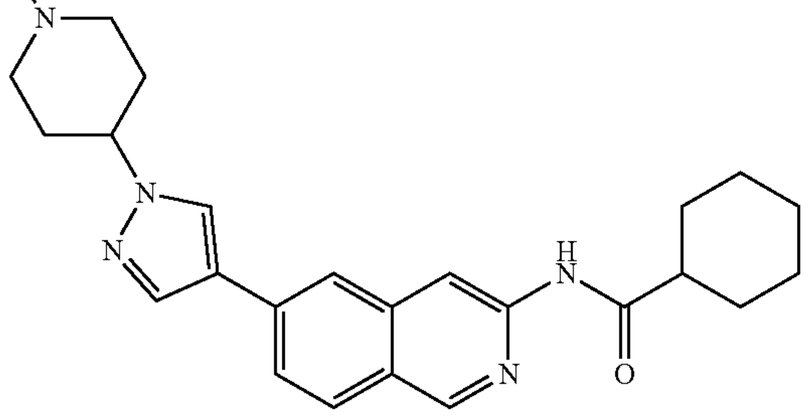
968



N-(8-Fluoro-6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(4-methylpiperazin-1-yl)acetamide 968

Beige solid (25.0 mg, 0.065 mmol, 23.1% yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 2.33 (3H, br s), 2.52-2.77 (8H, m), 3.27 (2H, s), 3.90 (3H, s), 7.62 (1H, dd, J=12.08, 1.37 Hz), 7.99 (1H, s), 8.14 (1H, d, J=0.82 Hz), 8.41 (1H, s), 8.48 (1H, s), 9.17 (1H, s), 10.12 (1H, br s); ESIMS found for $C_{20}H_{23}FN_6O$ m/z 383.2 (M+1).

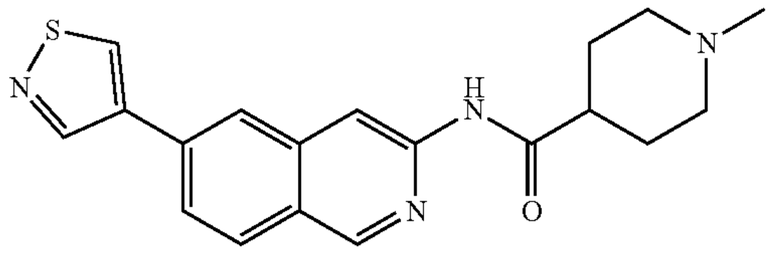
969



N-(6-(1-(1-Methylpiperidin-4-yl)-1H-pyrazol-4-yl) isoquinolin-3-yl) cyclohexanecarboxamide 969

Beige solid (79.0 mg, 0.189 mmol, 63.0% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.13-1.34 (3H, m), 1.39-1.51 (2H, m), 1.66 (1H, br d, J=11.25 Hz), 1.72-1.79 (2H, m), 1.82 (2H, br d, J=12.90 Hz), 1.94-2.11 (6H, m), 2.22 (3H, s), 2.52-2.60 (1H, m), 2.87 (2H, br d, J=11.25 Hz), 4.10-4.20 (1H, m), 7.77 (1H, dd, J=8.51, 1.37 Hz), 7.99 (1H, d, J=8.51 Hz), 8.05 (1H, s), 8.10 (1H, s), 8.43 (1H, s), 8.47 (1H, s), 9.01 (1H, s), 10.37 (1H, s) ESIMS found for $C_{25}H_{31}N_5O$ m/z 418.25 (M+1).

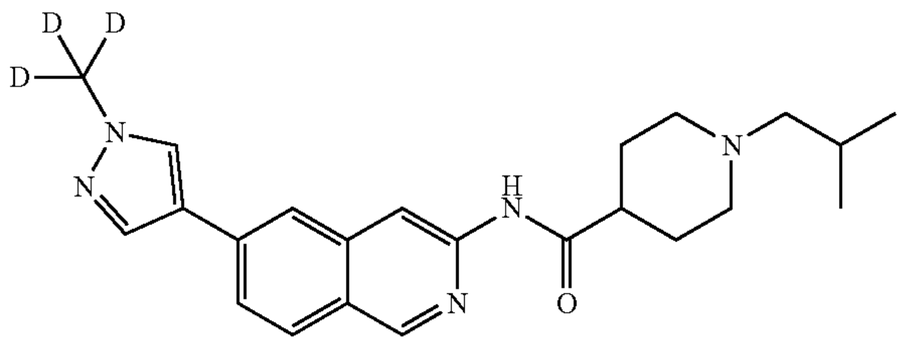
970



N-(6-(Isothiazol-4-yl)isoquinolin-3-yl)-1-methylpiperidine-4-carboxamide 970

Beige solid (28.0 mg, 0.079 mmol, 17.7% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.63-1.74 (2H, m), 1.75-1.84 (2H, m), 1.88 (2H, td, J=11.46, 2.06 Hz), 2.17 (3H, s), 2.51-2.57 (1H, m), 2.81 (2H, br d, J=11.53 Hz), 7.95 (1H, dd, J=8.51, 1.65 Hz), 8.11 (1H, d, J=8.51 Hz), 8.35 (1H, s), 8.54 (1H, s), 9.12 (1H, s), 9.25 (1H, s), 9.59 (1H, s), 10.49 (1H, s); ESIMS found for $C_{19}H_{20}N_4OS$ m/z 352.9 (M+1).

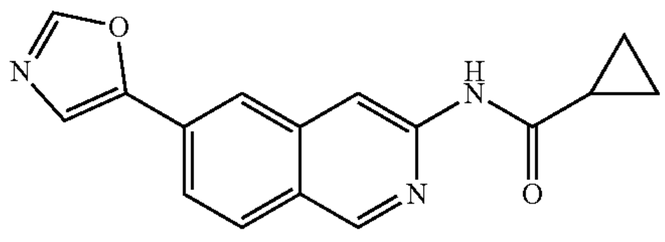
972



1-Isobutyl-N-(6-(1-(methyl-d3)-1H-pyrazol-4-yl)isoquinolin-3-yl)piperidine-4-carboxamide 972

White solid (165.0 mg, 0.418 mmol, 49.8% yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 0.86 (6H, d, J=6.59 Hz), 1.62-1.72 (2H, m), 1.73-1.81 (3H, m), 1.82-1.91 (2H, m), 2.02 (2H, d, J=7.41 Hz), 2.51-2.59 (1H, m), 2.81-2.90 (2H, m), 7.74 (1H, dd, J=8.51, 1.65 Hz), 8.00 (1H, d, J=8.51 Hz), 8.04 (1H, s), 8.08 (1H, d, J=0.82 Hz), 8.35 (1H, s), 8.44 (1H, s), 9.02 (1H, s), 10.45 (1H, s); ESIMS found for $C_{23}H_{26}[^2H_3]N_5O$ m/z 395.2 (M+1).

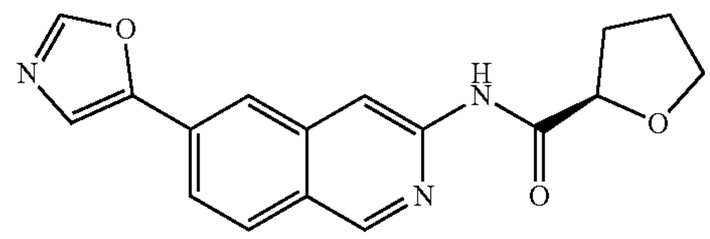
973



N-(6-(Oxazol-5-yl)isoquinolin-3-yl)cyclopropanecarboxamide 974

Beige solid (34.0 mg, 0.122 mmol, 25.7% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 0.78-0.91 (4H, m), 2.04-2.12 (1H, m), 7.86 (1H, dd, J=8.51, 1.65 Hz), 7.95 (1H, s), 8.13 (1H, d, J=8.78 Hz), 8.17 (1H, s), 8.50 (1H, s), 8.57 (1H, s), 9.14 (1H, s), 10.93 (1H, s); ESIMS found for $C_{16}H_{13}N_3O_2$ m/z 280.1 (M+1).

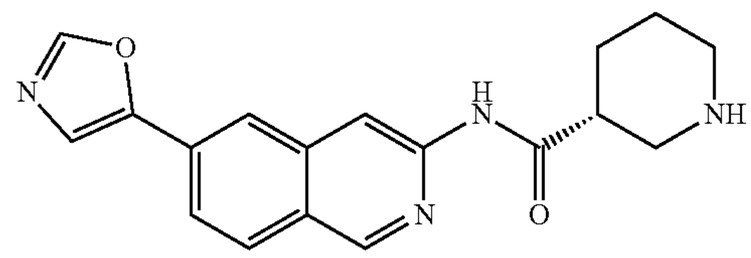
974



(R)—N-(6-(Oxazol-5-yl)isoquinolin-3-yl)tetrahydrofuran-2-carboxamide 974

Light yellow solid (120.0 mg, 0.388 mmol, 41.0% yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.83-1.97 (2H, m), 1.98-2.08 (1H, m), 2.20-2.31 (1H, m), 3.82-3.91 (1H, m), 3.97-4.06 (1H, m), 4.54 (1H, dd, J=8.37, 5.63 Hz), 7.90 (1H, dd, J=8.64, 1.51 Hz), 7.96 (1H, s), 8.16 (1H, d, J=8.51 Hz), 8.25 (1H, s), 8.52 (1H, s), 8.58 (1H, s), 9.15 (1H, s), 9.88 (1H, s); ESIMS found for $C_{17}H_{15}N_3O_3$ m/z 310.1 (M+1).

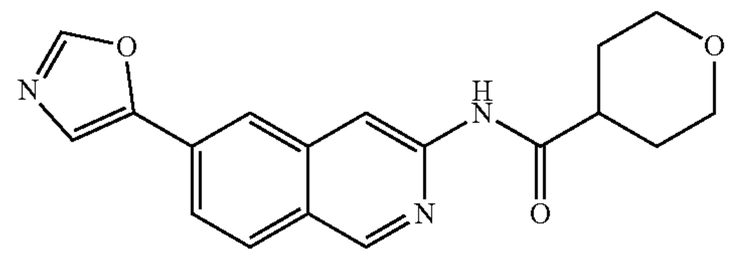
975



(R)—N-(6-(Oxazol-5-yl)isoquinolin-3-yl)piperidine-3-carboxamide 975

Beige solid (19.0 mg, 0.059 mmol, 24.9% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.36-1.47 (1H, m), 1.56-1.64 (1H, m), 1.64-1.72 (1H, m), 1.87 (1H, dt, J=8.58, 4.08 Hz), 2.52-2.59 (1H, m), 2.59-2.67 (1H, m), 2.75 (1H, br dd, J=11.94, 8.92 Hz), 2.78-2.85 (1H, m), 2.99 (1H, br dd, J=12.08, 3.02 Hz), 7.86 (1H, dd, J=8.51, 1.65 Hz), 7.95 (1H, s), 8.13 (1H, d, J=8.51 Hz), 8.19 (1H, s), 8.52 (1H, s), 8.58 (1H, s), 9.12 (1H, s), 10.85 (1H, s); ESIMS found for $C_{18}H_{18}N_4O_2$ m/z 323.0 (M+1).

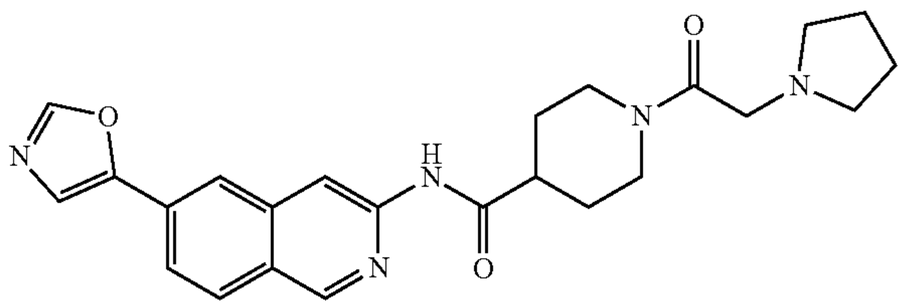
976



N-(6-(Oxazol-5-yl)isoquinolin-3-yl)tetrahydro-2H-pyran-4-carboxamide 976

Beige solid (17.5 mg, 0.054 mmol, 24.6% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.63-1.78 (4H, m), 2.78-2.87 (1H, m), 3.33-3.40 (2H, m), 3.88-3.96 (2H, m), 7.87 (1H, dd, J=8.64, 1.51 Hz), 7.95 (1H, s), 8.13 (1H, d, J=8.78 Hz), 8.20 (1H, s), 8.54 (1H, s), 8.58 (1H, s), 9.13 (1H, s), 10.60 (1H, s); ESIMS found for $C_{18}H_{17}N_3O_3$ m/z 323.9 (M+1).

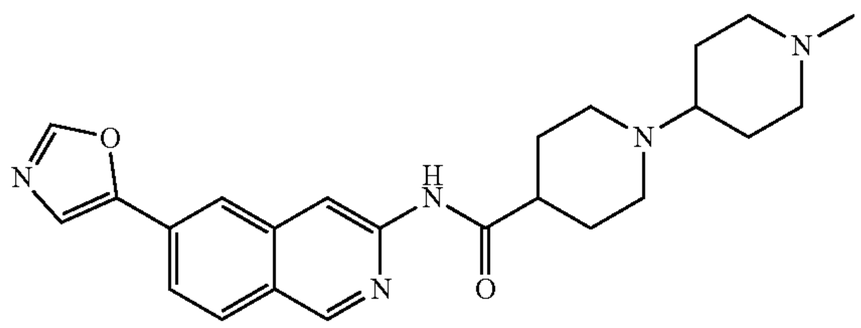
977



N-(6-(Oxazol-5-yl)isoquinolin-3-yl)-1-(2-(pyrrolidin-1-yl)acetyl)piperidine-4-carboxamide 977

White solid (33.4 mg, 0.077 mmol, 43.3% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.41-1.53 (1H, m), 1.55-1.66 (1H, m), 1.69 (4H, br s), 1.84 (2H, br d, J=10.98 Hz), 2.48 (4H, br s), 2.56-2.66 (1H, m), 2.82 (1H, ddt, J=11.25, 7.55, 3.91, 3.91 Hz), 3.01 (1H, br t, J=12.21 Hz), 3.14-3.21 (1H, m), 3.33-3.37 (1H, m), 4.11 (1H, br d, J=13.45 Hz), 4.40 (1H, br d, J=13.17 Hz), 7.87 (1H, dd, J=8.51, 1.10 Hz), 7.95 (1H, s), 8.13 (1H, d, J=8.51 Hz), 8.20 (1H, s), 8.53 (1H, s), 8.57 (1H, s), 9.14 (1H, s), 10.64 (1H, s); ESIMS found for $C_{24}H_{27}N_5O_3$ m/z 434.0 (M+1).

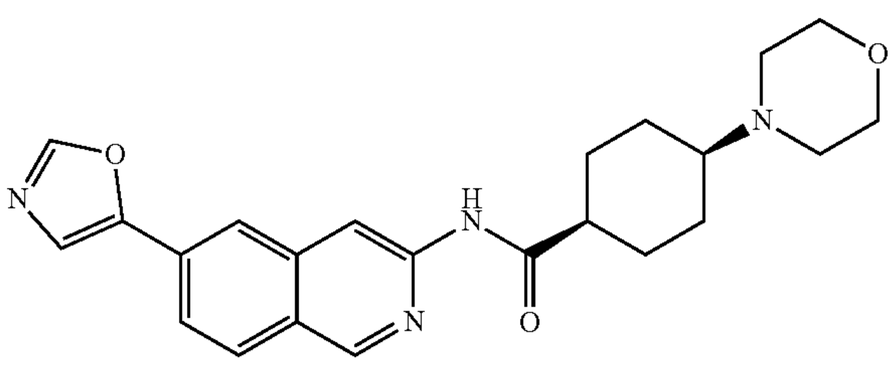
978



1'-Methyl-N-(6-(oxazol-5-yl)isoquinolin-3-yl)-[1,4'-bipiperidine]-4-carboxamide 978

Beige solid (90.0 mg, 0.215 mmol, 61.7% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.43 (2H, qd, J=11.85, 3.43 Hz), 1.58-1.71 (4H, m), 1.75-1.86 (4H, m), 2.07-2.20 (3H, m), 2.12 (3H, s), 2.51-2.57 (1H, m), 2.77 (2H, br d, J=11.53 Hz), 2.90 (2H, br d, J=11.25 Hz), 7.86 (1H, dd, J=8.51, 1.65 Hz), 7.94 (1H, s), 8.12 (1H, d, J=8.78 Hz), 8.19 (1H, s), 8.54 (1H, s), 8.57 (1H, s), 9.12 (1H, s), 10.53 (1H, s); ESIMS found for $C_{24}H_{29}N_5O_2$ m/z 420.2 (M+1).

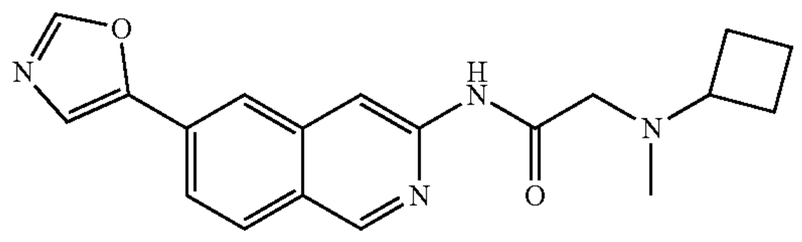
979



cis-4-Morpholino-N-(6-(oxazol-5-yl)isoquinolin-3-yl)cyclohexane-1-carboxamide 979

Off-white solid (125.0 mg, 0.308 mmol, 51.7% yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.15-1.27 (2H, m), 1.42-1.55 (2H, m), 1.91 (4H, br t, J=12.62 Hz), 2.17-2.26 (1H, m), 2.45-2.49 (4H, m), 2.51-2.53 (1H, m), 3.52-3.59 (4H, m), 7.86 (1H, dd, J=8.51, 1.37 Hz), 7.95 (1H, s), 8.12 (1H, d, J=8.51 Hz), 8.18 (1H, s), 8.52 (1H, s), 8.57 (1H, s), 9.12 (1H, s), 10.53 (1H, s); ESIMS found for $C_{23}H_{26}N_4O_3$ m/z 407.2 (M+1).

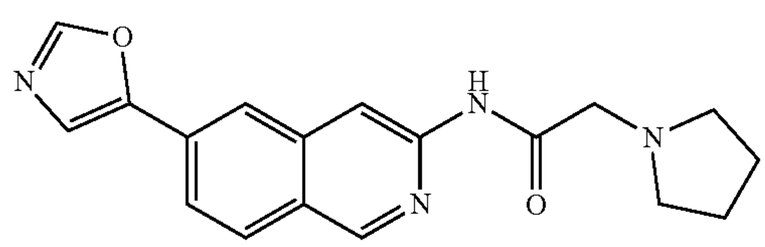
980



2-(Cyclobutyl(methyl)amino)-N-(6-(oxazol-5-yl)isoquinolin-3-yl)acetamide 980

Beige solid (31.5 mg, 0.094 mmol, 49.2% yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.54-1.69 (2H, m), 1.80-1.92 (2H, m), 1.98-2.06 (2H, m), 2.23 (3H, s), 3.03-3.11 (1H, m), 3.13 (2H, s), 7.89 (1H, dd, J=8.51, 1.65 Hz), 7.97 (1H, s), 8.16 (1H, d, J=8.51 Hz), 8.27 (1H, s), 8.53 (1H, s), 8.58 (1H, s), 9.15 (1H, s), 10.01 (1H, s); ESIMS found for $C_{19}H_{20}N_4O_2$ m/z 337.1 (M+1).

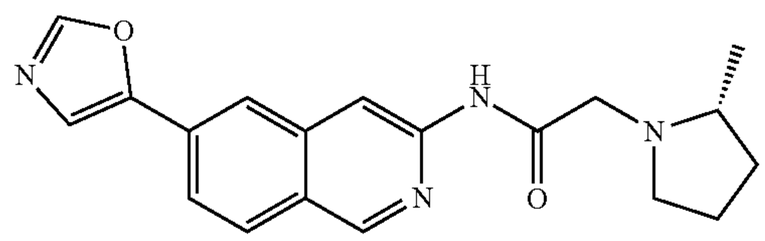
981



N-(6-(Oxazol-5-yl)isoquinolin-3-yl)-2-(pyrrolidin-1-yl)acetamide 981

Off-white solid (45.0 mg, 0.140 mmol, 42.3% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.78 (4H, dt, J=6.79, 3.33 Hz), 2.62-2.70 (4H, m), 3.37 (2H, s), 7.89 (1H, dd, J=8.78, 1.65 Hz), 7.96 (1H, s), 8.15 (1H, d, J=8.51 Hz), 8.26 (1H, s), 8.53 (1H, s), 8.58 (1H, s), 9.14 (1H, s), 10.01 (1H, s); ESIMS found for $C_{18}H_{18}N_4O_2$ m/z 323.1 (M+1).

982

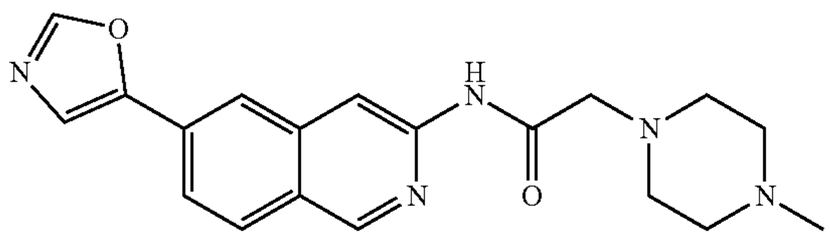


(R)-2-(2-Methylpyrrolidin-1-yl)-N-(6-(oxazol-5-yl)isoquinolin-3-yl) acetamide 982

Beige solid (8.0 mg, 0.024 mmol, 23.8% yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.09 (3H, d, J=6.04 Hz), 1.41 (1H, dddd, J=12.32, 10.39, 8.30, 6.31 Hz), 1.67-1.84 (2H, m), 1.91-2.02 (1H, m), 2.40 (1H, q, J=8.78 Hz), 2.57-2.66 (1H, m), 3.13 (1H, d, J=16.19 Hz), 3.13-3.20 (1H, m), 3.55 (1H, d, J=16.19 Hz), 7.89 (1H, dd, J=8.51, 1.65 Hz), 7.97 (1H, s), 8.16 (1H, d, J=8.51 Hz), 8.27 (1H, s), 8.53 (1H, s),

8.58 (1H, s), 9.14 (1H, s), 9.98 (1H, s); ESIMS found for $C_{19}H_{20}N_4O_2$ m/z 337.2 (M+1).

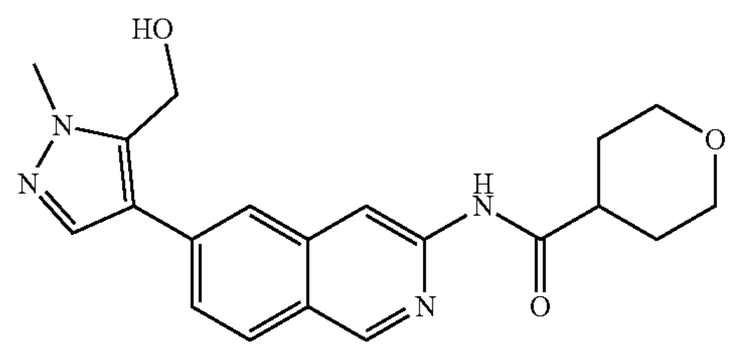
983



2-(4-Methylpiperazin-1-yl)-N-(6-(oxazol-5-yl)isoquinolin-3-yl)acetamide 983

Pale yellow solid (43.0 mg, 0.122 mmol, 37.1% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 2.19 (3H, s), 2.40 (4H, br s), 2.58 (4H, br s), 3.23 (2H, s), 7.89 (1H, dd, J=8.51, 1.65 Hz), 7.96 (1H, s), 8.15 (1H, d, J=8.78 Hz), 8.26 (1H, s), 8.53 (1H, s), 8.58 (1H, s), 9.15 (1H, s), 10.01 (1H, s); ESIMS found for $C_{19}H_{21}N_5O_2$ m/z 352.2 (M+1).

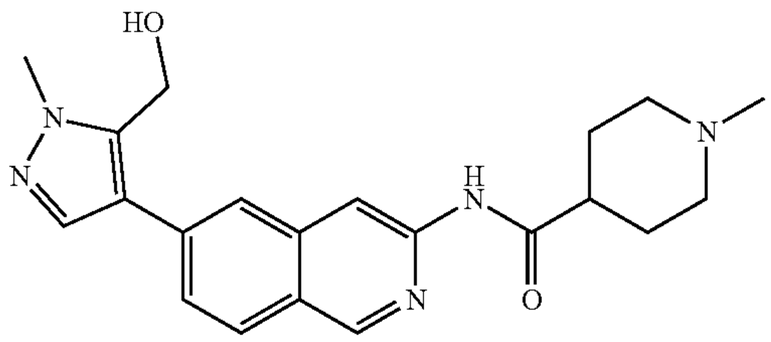
984



N-(6-(5-(Hydroxymethyl)-1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl) tetrahydro-2H-pyran-4-carboxamide 984

Beige solid (30.0 mg, 0.082 mmol, 25.9% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.63-1.79 (4H, m), 2.77-2.87 (1H, m), 3.33-3.40 (2H, m), 3.91 (2H, br d, J=2.47 Hz), 3.93 (3H, s), 4.64 (2H, d, J=5.21 Hz), 5.56 (1H, t, J=5.35 Hz), 7.68 (1H, dd, J=8.51, 1.37 Hz), 7.81 (1H, s), 7.94 (1H, s), 8.05 (1H, d, J=8.51 Hz), 8.48 (1H, s), 9.09 (1H, s), 10.54 (1H, s); ESIMS found for $C_{20}H_{22}N_4O_3$ m/z 367.0 (M+1).

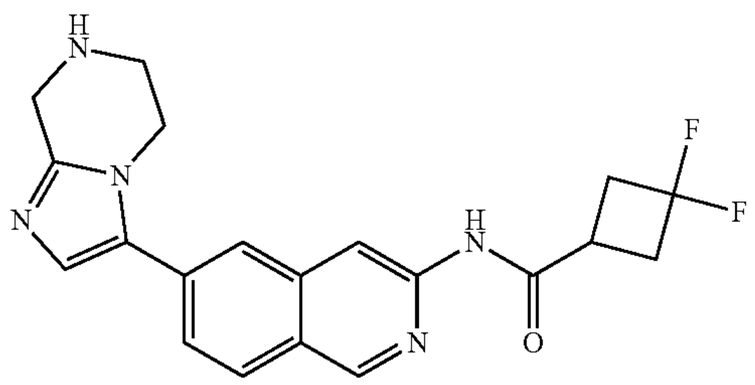
985



N-(6-(5-(Hydroxymethyl)-1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-1-methylpiperidine-4-carboxamide 985

Beige solid (26.0 mg, 0.069 mmol, 12.9% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.62-1.73 (2H, m), 1.74-1.81 (2H, m), 1.86 (2H, td, J=11.60, 2.06 Hz), 2.16 (3H, s), 2.46-2.55 (1H, m), 2.77-2.85 (2H, m), 3.93 (3H, s), 4.63 (2H, d, J=5.21 Hz), 5.56 (1H, t, J=5.35 Hz), 7.67 (1H, dd, J=8.51, 1.65 Hz), 7.81 (1H, s), 7.94 (1H, s), 8.05 (1H, d, J=8.51 Hz), 8.48 (1H, s), 9.08 (1H, s), 10.50 (1H, s); ESIMS found for $C_{21}H_{25}N_5O_2$ m/z 380.0 (M+1).

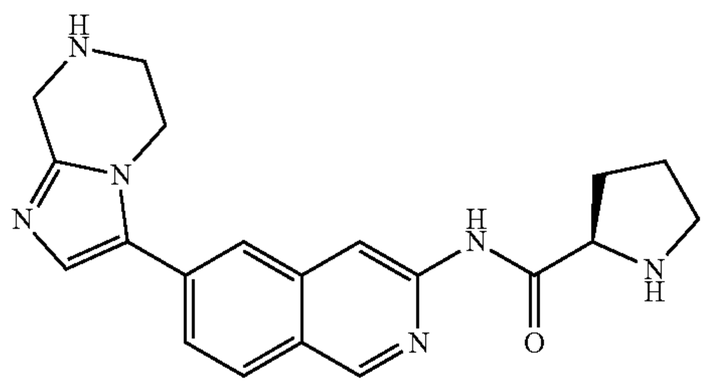
986



3,3-Difluoro-N-(6-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-3-yl) isoquinolin-3-yl)cyclobutane-1-carboxamide 986

White solid (33.0 mg, 0.086 mmol, 28.3% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 2.75-2.90 (5H, m), 3.07 (2H, br t, J=5.21 Hz), 3.95 (2H, s), 4.11 (2H, t, J=5.35 Hz), 7.30 (1H, s), 7.68 (1H, dd, J=8.51, 1.65 Hz), 7.97 (1H, s), 8.07 (1H, d, J=8.51 Hz), 8.55 (1H, s), 9.11 (1H, s), 10.78 (1H, s); ESIMS found for $C_{20}H_{19}F_2N_5O$ m/z 384.15 (M+1).

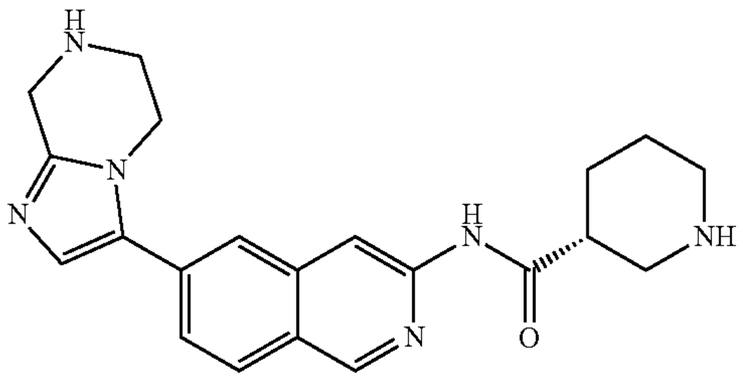
987



(R)—N-(6-(5,6,7,8-Tetrahydroimidazo[1,2-a]pyrazin-3-yl)isoquinolin-3-yl) pyrrolidine-2-carboxamide 987

Beige solid (20.0 mg, 0.055 mmol, 34.3% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.67 (2H, quin, J=6.72 Hz), 1.78-1.90 (1H, m), 2.05-2.16 (1H, m), 2.87 (1H, dt, J=10.15, 6.45 Hz), 2.97 (1H, dt, J=10.15, 6.72 Hz), 3.07 (2H, t, J=5.49 Hz), 3.81 (1H, dd, J=9.06, 5.49 Hz), 3.95 (2H, s), 4.12 (2H, t, J=5.35 Hz), 7.30 (1H, s), 7.67 (1H, dd, J=8.51, 1.65 Hz), 7.98 (1H, s), 8.07 (1H, d, J=8.78 Hz), 8.52 (1H, s), 9.09 (1H, s), 10.38 (1H, s); ESIMS found for $C_{20}H_{22}N_6O$ m/z 363.2 (M+1).

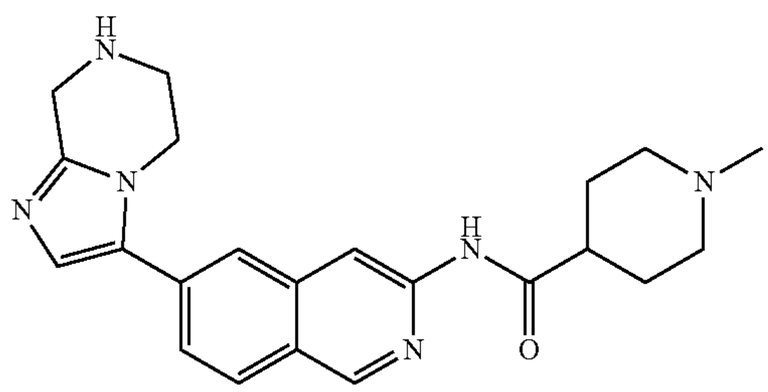
988



(R)—N-(6-(5,6,7,8-Tetrahydroimidazo[1,2-a] pyrazin-3-yl)isoquinolin-3-yl) piperidine-3-carboxamide 988

Dark brown gum (36.0 mg, 0.096 mmol, 55.2% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.31-1.56 (2H, m), 1.57-1.74 (2H, m), 2.32-2.46 (1H, m), 2.52-2.66 (2H, m), 2.70-2.88 (2H, m), 3.07 (2H, t, J=5.35 Hz), 3.95 (2H, s), 4.11 (2H, t, J=5.21 Hz), 7.29 (1H, s), 7.65 (1H, dd, J=8.51, 1.65 Hz), 7.93 (1H, s), 8.05 (1H, d, J=8.51 Hz), 8.51 (1H, s), 9.08 (1H, s), 10.79 (1H, s); ESIMS found for $C_{21}H_{24}N_6O$ m/z 377.0 (M+1).

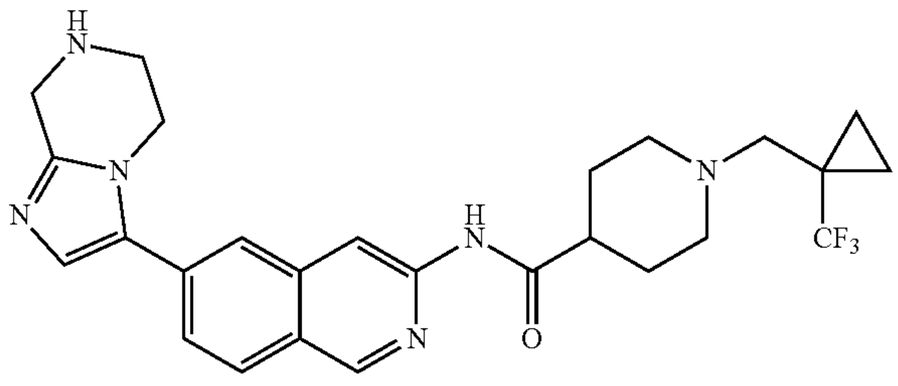
989



1-Methyl-N-(6-(5,6,7,8-tetrahydroimidazo[1,2-a] pyrazin-3-yl)isoquinolin-3-yl)piperidine-4-carboxamide 989

White solid (3.0 mg, 0.008 mmol, 6.4% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.61-1.72 (2H, m), 1.73-1.80 (2H, m), 1.87 (2H, td, J=11.60, 2.06 Hz), 2.16 (3H, s), 2.51-2.56 (1H, m), 2.76-2.86 (3H, m), 3.07 (2H, br t, J=5.21 Hz), 3.95 (2H, s), 4.10 (2H, t, J=5.49 Hz), 7.28 (1H, s), 7.65 (1H, dd, J=8.51, 1.65 Hz), 7.93 (1H, s), 8.05 (1H, d, J=8.51 Hz), 8.52 (1H, s), 9.09 (1H, s), 10.51 (1H, s); ESIMS found for $C_{22}H_{26}N_6O$ m/z 391.2 (M+1).

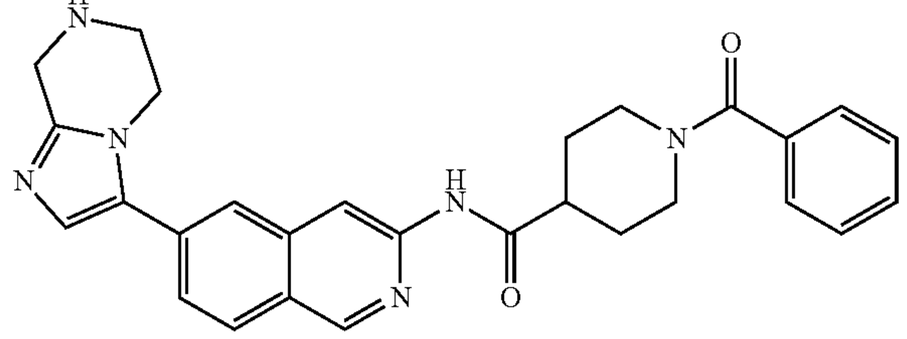
990



tert-Butyl 6-((6-(1-methyl-5-(piperidin-1-ylmethyl)-1H-pyrazol-4-yl) isoquinolin-3-yl)carbamoyl)-2-azaspiro[3.3]heptane-2-carboxylate 992

White solid (200.0 mg, 0.367 mmol, 78.3% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.37 (11H, s), 1.45-1.54 (4H, m), 2.37 (4H, s), 2.38 (4H, s), 3.21-3.30 (1H, m), 3.65 (2H, s), 3.81 (2H, br s), 3.88 (2H, br s), 3.91 (3H, s), 7.69 (1H, dd, J=8.51, 1.65 Hz), 7.80 (1H, s), 8.02 (1H, d, J=8.78 Hz), 8.05 (1H, s), 8.47 (1H, s), 9.06 (1H, s), 10.44 (1H, s); ESIMS found for $C_{31}H_{40}N_6O_3$ m/z 545.3 (M+1).

991

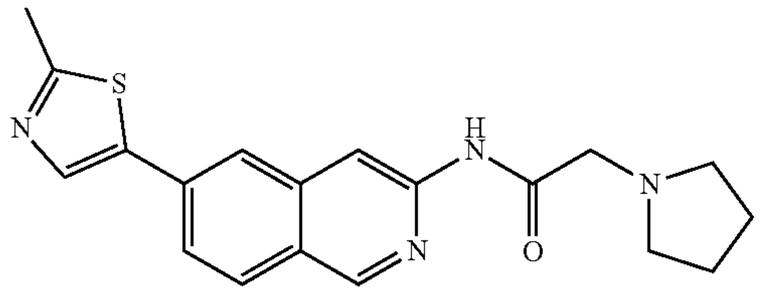


1-Benzoyl-N-(6-(5,6,7,8-tetrahydroimidazo[1,2-a] pyrazin-3-yl)isoquinolin-3-yl)piperidine-4-carboxamide 991

White solid (27.7 mg, 0.058 mmol, 70.8% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.63 (2H, br s), 1.75-1.98 (2H, m), 2.69-2.96 (1H, m), 2.86 (2H, ddt, J=11.22, 7.51, 3.81, 3.81 Hz), 3.02-3.17 (1H, m), 3.07 (2H, brt, J=5.08 Hz), 3.95 (2H, s), 4.11 (2H, t, J=5.21 Hz), 7.29 (1H, s), 7.36-7.43 (2H, m), 7.43-7.50 (3H, m), 7.66 (1H, dd, J=8.51, 1.65 Hz), 7.94 (1H, s), 8.06 (1H, d, J=8.78 Hz), 8.52 (1H, s), 9.10 (1H, s), 10.61 (1H, s); ESIMS found for $C_{28}H_{28}N_6O_2$ m/z 481.2 (M+1).

992

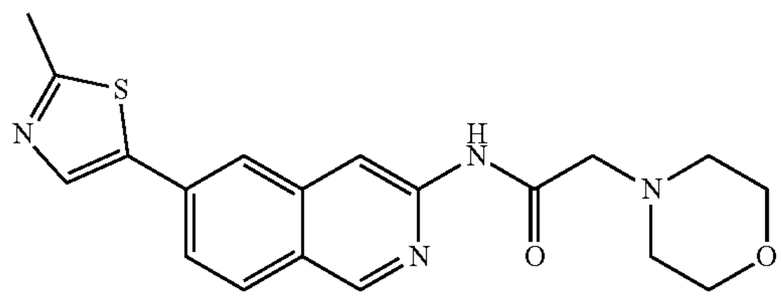
993



N-(6-(2-Methylthiazol-5-yl)isoquinolin-3-yl)-2-(pyrrolidin-1-yl)acetamide 993

Beige solid (25.0 mg, 0.071 mmol, 21.6% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.78 (4H, dt, J=6.79, 3.33 Hz), 2.62-2.69 (4H, m), 2.72 (3H, s), 3.36 (2H, s), 7.82 (1H, dd, J=8.51, 1.92 Hz), 8.10 (1H, d, J=8.51 Hz), 8.15 (1H, d, J=0.82 Hz), 8.30 (1H, s), 8.50 (1H, s), 9.11 (1H, s), 9.99 (1H, s); ESIMS found for $C_{19}H_{20}N_4OS$ m/z 353.1 (M+1).

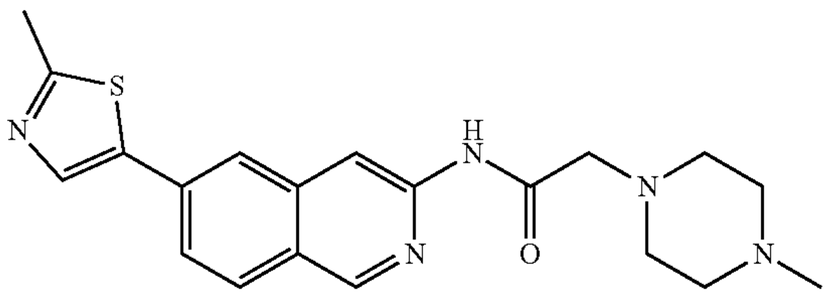
994



N-(6-(2-Methylthiazol-5-yl)isoquinolin-3-yl)-2-morpholinoacetamide 994

Beige solid (44.0 mg, 0.119 mmol, 41.8% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 2.55-2.61 (4H, m), 2.72 (3H, s), 3.25 (2H, s), 3.60-3.68 (4H, m), 7.82 (1H, dd, J=8.64, 1.78 Hz), 8.10 (1H, d, J=8.51 Hz), 8.15 (1H, d, J=0.82 Hz), 8.30 (1H, s), 8.50 (1H, s), 9.12 (1H, s), 10.08 (1H, s); ESIMS found for $C_{19}H_{20}N_4O_2S$ m/z 369.1 (M+1).

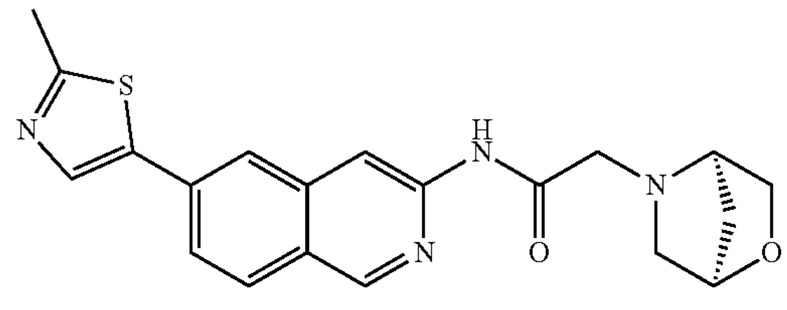
995



2-(4-Methylpiperazin-1-yl)-N-(6-(2-methylthiazol-5-yl)isoquinolin-3-yl) acetamide 995

Brown solid (31.0 mg, 0.081 mmol, 31.3% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 2.19 (3H, s), 2.40 (4H, br s), 2.58 (4H, br s), 2.72 (3H, s), 3.23 (2H, s), 7.82 (1H, dd, J=8.51, 1.65 Hz), 8.10 (1H, d, J=8.51 Hz), 8.15 (1H, s), 8.30 (1H, s), 8.50 (1H, s), 9.12 (1H, s), 10.00 (1H, s); ESIMS found for $C_{20}H_{23}N_5OS$ m/z 382.2 (M+1).

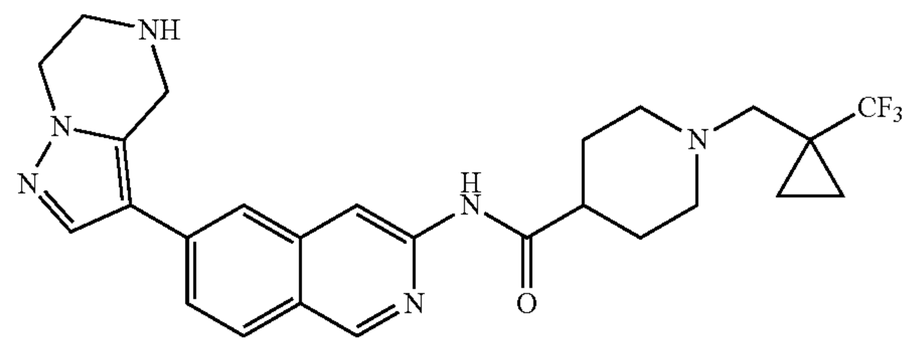
996



2-((1R,4R)-2-Oxa-5-azabicyclo[2.2.1]heptan-5-yl)-N-(6-(2-methylthiazol-5-yl)isoquinolin-3-yl)acetamide 996

Beige solid (50.0 mg, 0.131 mmol, 43.8% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.64-1.71 (1H, m), 1.87 (1H, dd, J=9.47, 1.78 Hz), 2.63 (1H, d, J=9.88 Hz), 2.72 (3H, s), 2.95 (1H, dd, J=9.88, 1.65 Hz), 3.46 (2H, d, J=4.39 Hz), 3.59 (1H, dd, J=7.68, 1.92 Hz), 3.63 (1H, s), 3.88 (1H, d, J=7.68 Hz), 4.41 (1H, s), 7.82 (1H, dd, J=8.64, 1.78 Hz), 8.10 (1H, d, J=8.51 Hz), 8.15 (1H, d, J=0.82 Hz), 8.30 (1H, s), 8.50 (1H, s), 9.12 (1H, s), 9.98 (1H, s); ESIMS found for $C_{20}H_{20}N_4O_2S$ m/z 381.1 (M+1).

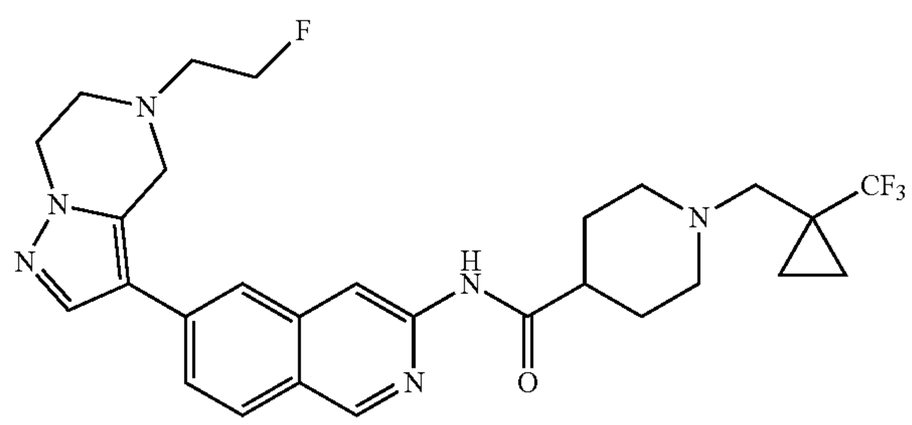
997



N-(6-(4,5,6,7-Tetrahydropyrazolo[1,5-a]pyrazin-3-yl)isoquinolin-3-yl)-1-((1-(trifluoromethyl)cyclopropyl)methyl)piperidine-4-carboxamide 997

Tan solid (33.6 mg, 0.067 mmol, 47.8% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 0.73 (2H, br s), 0.94-0.99 (2H, m), 1.62-1.72 (2H, m), 1.74-1.81 (2H, m), 1.91-1.99 (2H, m), 2.53-2.58 (1H, m), 2.93-2.99 (2H, m), 3.16 (2H, br t, J=5.21 Hz), 4.06 (2H, br t, J=5.35 Hz), 4.22 (2H, s), 7.63 (1H, dd, J=8.51, 1.65 Hz), 7.76 (1H, s), 7.98 (1H, s), 8.01 (1H, d, J=8.51 Hz), 8.47 (1H, s), 9.04 (1H, s), 10.46 (1H, s); ESIMS found for $C_{26}H_{29}F_3N_6O$ m/z 499.25 (M+1).

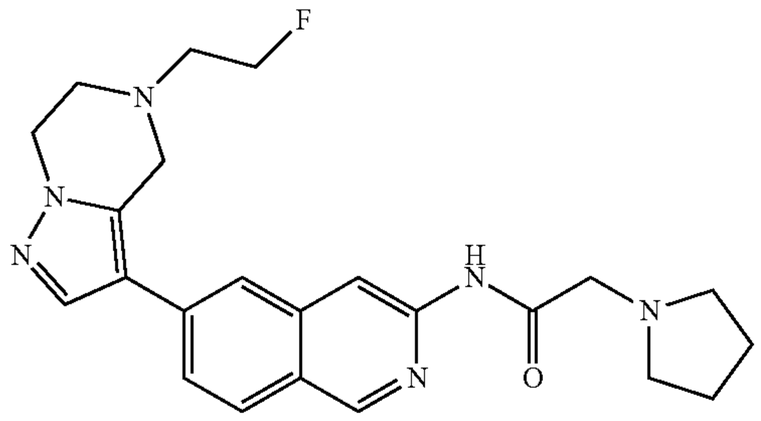
998



N-(6-(5-(2-Fluoroethyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-3-yl)isoquinolin-3-yl)-1-((1-(trifluoromethyl)cyclopropyl)methyl)piperidine-4-carboxamide 998

Off-white solid (15.0 mg, 0.028 mmol, 41.6% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 0.73 (2H, br s), 0.94-0.99 (2H, m), 1.62-1.72 (2H, m), 1.74-1.82 (2H, m), 1.91-1.99 (2H, m), 2.52-2.59 (1H, m), 2.93-3.03 (4H, m), 3.07 (2H, t, J=5.35 Hz), 4.08 (2H, s), 4.18 (2H, t, J=5.49 Hz), 4.66 (2H, dt, J=47.85, 4.70 Hz), 7.64 (1H, dd, J=8.51, 1.37 Hz), 7.76 (1H, s), 8.00 (1H, s), 8.02 (1H, d, J=8.51 Hz), 8.48 (1H, s), 9.05 (1H, s), 10.48 (1H, s); ESIMS found for $C_{28}H_{32}F_4N_6O$ m/z 545.3 (M+1).

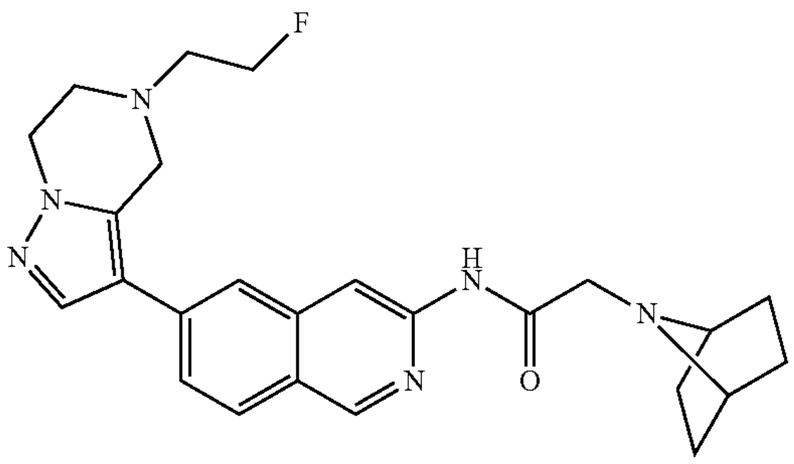
999



N-(6-(5-(2-Fluoroethyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-3-yl) isoquinolin-3-yl)-2-(pyrrolidin-1-yl)acetamide 999

Yellow oil (5.6 mg, 0.013 mmol, 38.4% yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.78 (4H, dt, J=6.72, 3.22 Hz), 2.66 (4H, br s), 2.98 (3H, dt, J=28.55, 4.95 Hz), 3.07 (2H, t, J=5.49 Hz), 3.36 (2H, s), 4.09 (2H, s), 4.18 (2H, t, J=5.49 Hz), 4.66 (3H, dt, J=47.75, 4.95 Hz), 7.65 (1H, dd, J=8.51, 1.65 Hz), 7.82 (1H, s), 8.01 (1H, s), 8.05 (1H, d, J=8.51 Hz), 8.47 (1H, s), 9.06 (1H, s), 9.96 (1H, s); ESIMS found for $C_{23}H_{27}FN_6O$ m/z 423.2 (M+1).

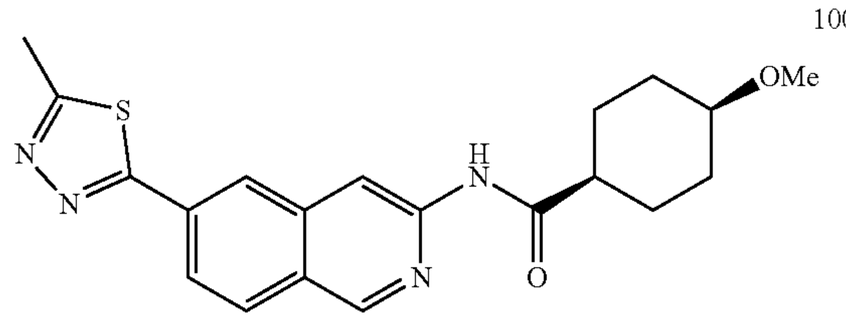
1000



2-(7-Azabicyclo[2.2.1]heptan-7-yl)-N-(6-(5-(2-fluoroethyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-3-yl)isoquinolin-3-yl)acetamide 1000

Yellow solid (26.5 mg, 0.059 mmol, 52.7% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.35 (4H, br d, J=6.86 Hz), 1.69-1.79 (4H, m), 2.99 (2H, dt, J=28.90, 4.95 Hz), 3.08 (2H, br t, J=5.49 Hz), 3.19 (2H, s), 3.36 (2H, br s), 4.09 (2H, s), 4.18 (2H, br t, J=5.49 Hz), 4.66 (2H, dt, J=47.85, 4.95 Hz), 7.65 (1H, dd, J=8.51, 1.65 Hz), 7.82 (1H, s), 8.00 (1H, s), 8.05 (1H, d, J=8.78 Hz), 8.48 (1H, s), 9.06 (1H, s), 10.08 (1H, s); ESIMS found for $C_{25}H_{29}FN_6O$ m/z 449.25 (M+1).

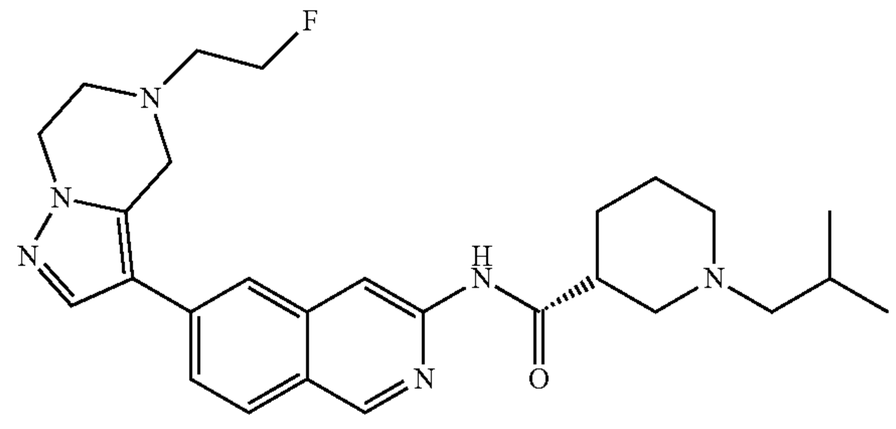
1001



cis-4-Methoxy-N-(6-(5-methyl-1,3,4-thiadiazol-2-yl) isoquinolin-3-yl) cyclohexane-1-carboxamide 1001

White solid (33.4 mg, 0.087 mmol, 21.2% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.08-1.18 (2H, m), 1.45-1.55 (2H, m), 1.88-1.94 (2H, m), 2.05-2.11 (2H, m), 2.52-2.58 (1H, m), 2.83 (3H, s), 3.09-3.16 (1H, m), 3.25 (3H, s), 8.09 (1H, dd, J=8.65, 1.51 Hz), 8.19 (1H, d, J=8.51 Hz), 8.44 (1H, s), 8.60 (1H, s), 9.21 (1H, s), 10.60 (1H, s); ESIMS found for $C_{20}H_{22}N_4O_2S$ m/z 383.15 (M+1).

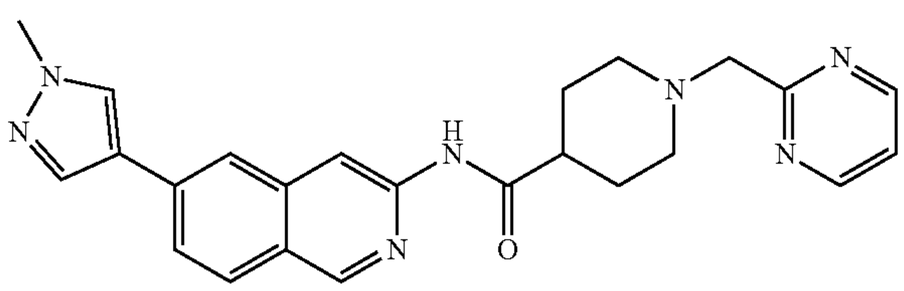
1002



(R)—N-(6-(5-(2-Fluoroethyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-3-yl) isoquinolin-3-yl)-1-isobutylpiperidine-3-carboxamide 1002

Light yellow gum (31.1 mg, 0.065 mmol, 40.7% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 0.89 (6H, dd, J=11.11, 6.45 Hz), 1.50-1.58 (2H, m), 1.69 (1H, br dd, J=8.37, 3.98 Hz), 1.78-1.86 (2H, m), 2.11 (1H, d, J=7.14 Hz), 2.09-2.17 (1H, m), 2.28-2.37 (1H, m), 2.60-2.66 (1H, m), 2.75-2.84 (2H, m), 2.98 (3H, dt, J=28.60, 4.95 Hz), 3.07 (2H, brt, J=5.49 Hz), 4.07 (2H, s), 4.18 (2H, t, J=5.35 Hz), 4.66 (2H, dt, J=47.80, 4.95 Hz), 7.64 (1H, dd, J=8.51, 1.65 Hz), 7.75 (1H, s), 8.00 (1H, s), 8.02 (1H, d, J=8.78 Hz), 8.46 (1H, s), 9.05 (1H, s), 10.69 (1H, s); ESIMS found for $C_{27}H_{35}FN_6O$ m/z 479.3 (M+1).

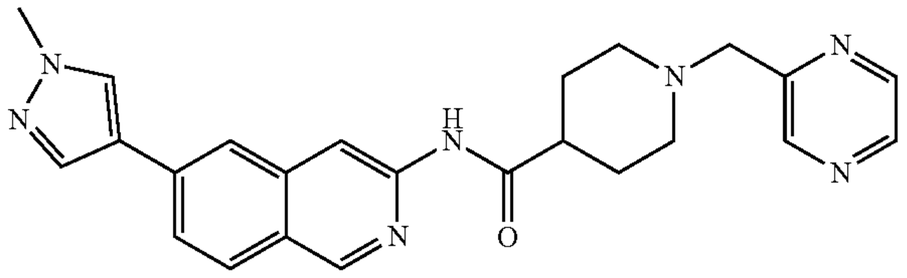
1003



N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-1-(pyrimidin-2-ylmethyl)piperidine-4-carboxamide 1003

Beige solid (75.0 mg, 0.175 mmol, 29.4% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.63-1.74 (2H, m), 1.74-1.82 (2H, m), 2.18 (2H, brt, J=10.70 Hz), 2.52-2.59 (1H, m), 2.98 (2H, br d, J=10.98 Hz), 3.74 (2H, s), 3.90 (3H, s), 7.41 (1H, t, J=4.80 Hz), 7.74 (1H, dd, J=8.51, 1.65 Hz), 7.99 (1H, d, J=8.51 Hz), 8.03 (1H, s), 8.07 (1H, d, J=0.82 Hz), 8.34 (1H, s), 8.44 (1H, s), 8.79 (2H, d, J=4.94 Hz), 9.02 (1H, s), 10.44 (1H, s); ESIMS found for $C_{24}H_{25}N_7O$ m/z 428.2 (M+1).

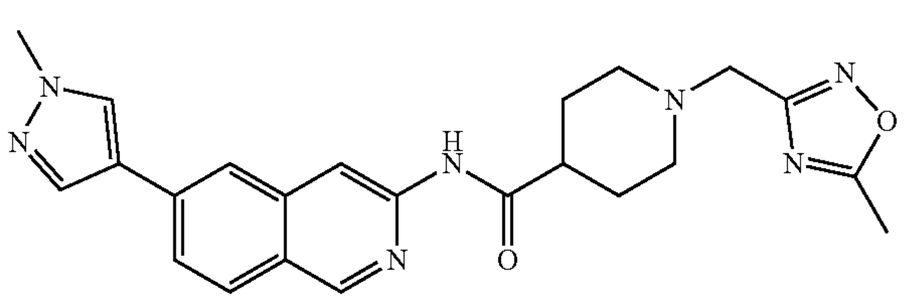
1004



N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-1-(pyrazin-2-ylmethyl)piperidine-4-carboxamide 1004

Orange solid (20.0 mg, 0.047 mmol, 7.8% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.66-1.76 (2H, m), 1.76-1.83 (2H, m), 2.09 (2H, td, J=11.60, 2.33 Hz), 2.52-2.61 (1H, m), 2.90 (2H, br d, J=11.53 Hz), 3.67 (2H, s), 3.90 (3H, s), 7.74 (1H, dd, J=8.51, 1.65 Hz), 7.99 (1H, d, J=8.51 Hz), 8.03 (1H, s), 8.07 (1H, s), 8.35 (1H, s), 8.44 (1H, s), 8.54 (1H, d, J=2.74 Hz), 8.58 (1H, dd, J=2.61, 1.51 Hz), 8.70 (1H, d, J=1.37 Hz), 9.02 (1H, s), 10.46 (1H, s); ESIMS found for $C_{24}H_{25}N_7O$ m/z 428.2 (M+1).

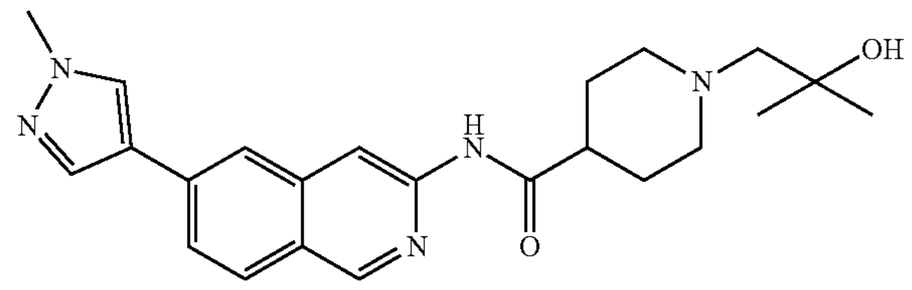
1005



1-((5-Methyl-1,2,4-oxadiazol-3-yl)methyl)-N-(6-(1-methyl-1H-pyrazol-4-yl) isoquinolin-3-yl)piperidine-4-carboxamide 1005

White solid (45.0 mg, 0.104 mmol, 17.5% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.63-1.74 (2H, m), 1.78-1.84 (2H, m), 2.18 (2H, td, J=11.53, 2.20 Hz), 2.35 (3H, s), 2.52-2.57 (1H, m), 2.89-2.96 (2H, m), 3.87 (2H, s), 3.90 (3H, s), 7.74 (1H, dd, J=8.51, 1.65 Hz), 8.00 (1H, d, J=8.51 Hz), 8.03 (1H, s), 8.07 (1H, s), 8.34 (1H, s), 8.44 (1H, s), 9.02 (1H, s), 10.45 (1H, s); ESIMS found for $C_{23}H_{25}N_7O_2$ m/z 432.2 (M+1).

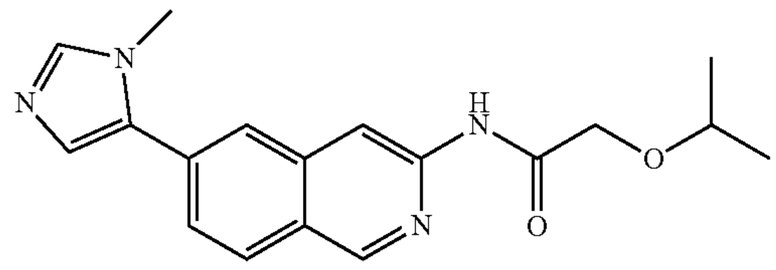
1006



1-(2-Hydroxy-2-methylpropyl)-N-(6-(1-methyl-1H-pyrazol-4-yl) isoquinolin-3-yl)piperidine-4-carboxamide 1006

White solid (45.0 mg, 0.110 mmol, 18.5% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.09 (6H, s), 1.72 (4H, br d, J=2.74 Hz), 2.13 (2H, br s), 2.20 (2H, br s), 2.46-2.55 (1H, m), 2.99 (2H, br d, J=9.88 Hz), 3.90 (3H, s), 4.04 (1H, br s), 7.74 (1H, dd, J=8.51, 1.65 Hz), 7.99 (1H, d, J=8.51 Hz), 8.04 (1H, s), 8.08 (1H, d, J=0.82 Hz), 8.35 (1H, s), 8.44 (1H, s), 9.02 (1H, s), 10.44 (1H, s); ESIMS found for $C_{23}H_{29}N_5O_2$ m/z 408.2 (M+1).

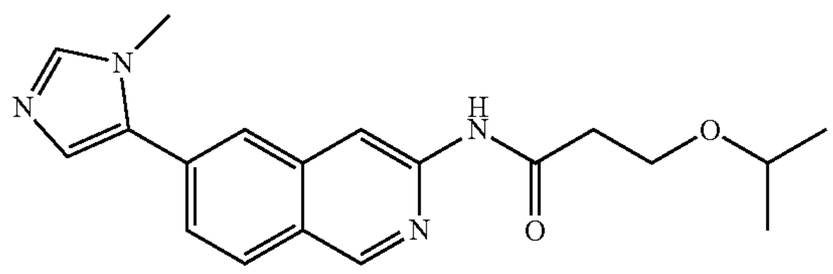
1008



2-Isopropoxy-N-(6-(1-methyl-1H-imidazol-5-yl) isoquinolin-3-yl)acetamide 1008

White solid (35.0 mg, 0.108 mmol, 18.6% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.20 (6H, d, J=6.04 Hz), 3.75 (1H, spt, J=6.13 Hz), 3.91 (3H, s), 4.15 (2H, s), 7.69 (1H, s), 7.73 (1H, dd, J=8.37, 1.78 Hz), 8.17 (1H, br s), 8.18 (1H, d, J=8.78 Hz), 8.51 (1H, s), 8.57 (1H, s), 9.20 (1H, s), 9.80 (1H, s); ESIMS found for $C_{18}H_{20}N_4O_2$ m/z 325.2 (M+1).

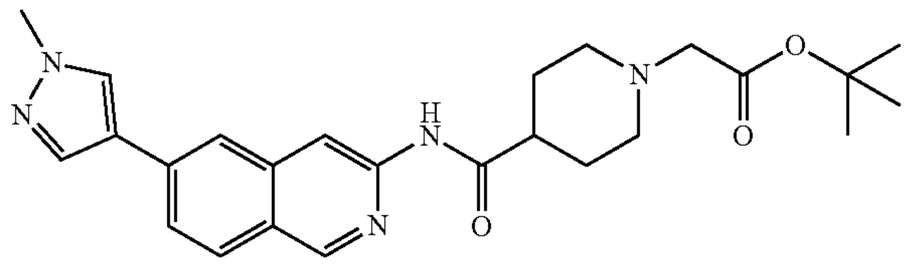
1009



3-Isopropoxy-N-(6-(1-methyl-1H-imidazol-5-yl) isoquinolin-3-yl) propanamide 1009

White solid (105.0 mg, 0.310 mmol, 43.5% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.08 (6H, d, J=6.04 Hz), 2.66 (2H, t, J=6.31 Hz), 3.58 (1H, spt, J=6.08 Hz), 3.69 (2H, t, J=6.17 Hz), 3.84 (3H, s), 7.34 (1H, s), 7.67 (1H, dd, J=8.51, 1.65 Hz), 7.87 (1H, s), 8.03 (1H, d, J=0.82 Hz), 8.09 (1H, d, J=8.51 Hz), 8.55 (1H, s), 9.13 (1H, s), 10.55 (1H, s); ESIMS found for $C_{19}H_{22}N_4O_2$ m/z 339.2 (M+1).

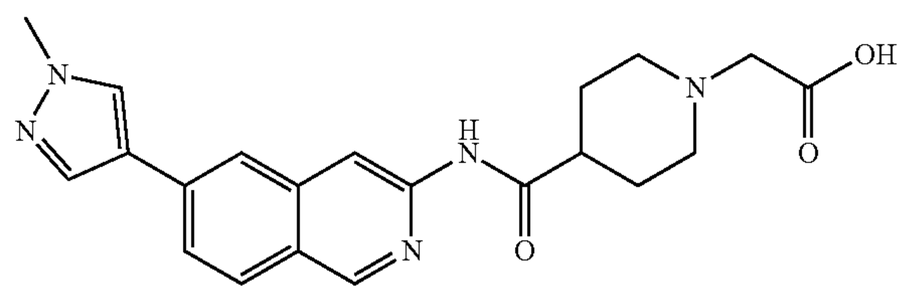
1010



tert-Butyl 2-(4-((6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl) carbamoyl) piperidin-1-yl)acetate 1010

White solid (75.0 mg, 0.167 mmol, 18.7% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.42 (9H, s), 1.62-1.73 (2H, m), 1.74-1.81 (2H, m), 2.22 (2H, td, J=11.53, 2.20 Hz), 2.51-2.57 (1H, m), 2.83-2.91 (2H, m), 3.10 (2H, s), 3.90 (3H, s), 7.74 (1H, dd, J=8.51, 1.65 Hz), 8.00 (1H, d, J=8.51 Hz), 8.03 (1H, s), 8.07 (1H, s), 8.34 (1H, s), 8.44 (1H, s), 9.02 (1H, s), 10.46 (1H, s); ESIMS found for $C_{25}H_{31}N_5O_3$ m/z 450.2 (M+1).

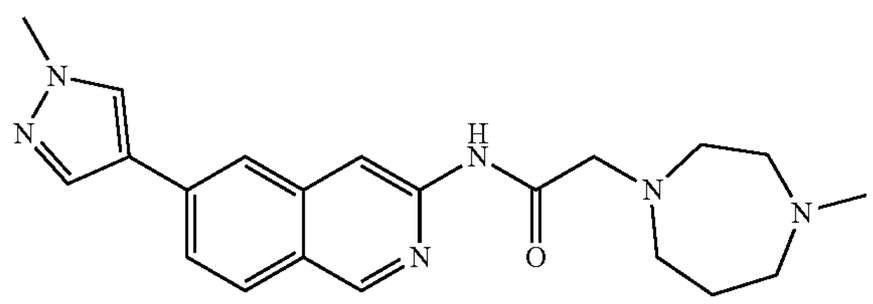
1011



2-(4-((6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)carbamoyl)piperidin-1-yl)acetic acid 1011

White solid. ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.76-1.90 (4H, m), 2.41-2.48 (2H, m), 2.57-2.66 (1H, m), 3.10-3.19 (4H, m), 3.90 (3H, s), 7.75 (1H, dd, J=8.51, 1.65 Hz), 8.00 (1H, d, J=8.51 Hz), 8.04 (1H, s), 8.08 (1H, s), 8.36 (1H, br s), 8.44 (1H, s), 9.03 (1H, s), 10.53 (1H, s); ESIMS found for $C_{21}H_{23}N_5O_3$ m/z 394.2 (M+1).

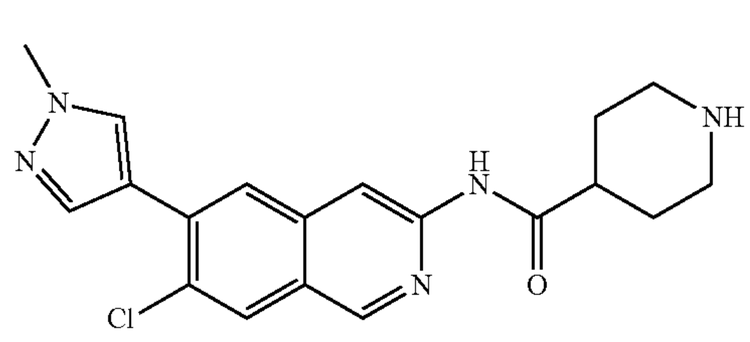
1012



2-(4-Methyl-1,4-diazepan-1-yl)-N-(6-(1-methyl-1H-pyrazol-4-yl) isoquinolin-3-yl)acetamide 1012

Off-white solid (40.0 mg, 0.106 mmol, 48.0% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.78 (2H, quip, J=5.97 Hz), 2.28 (3H, s), 2.56-2.64 (4H, m), 2.79-2.87 (4H, m), 3.36 (2H, s), 3.90 (3H, s), 7.77 (1H, dd, J=8.51, 1.65 Hz), 8.02 (1H, d, J=8.51 Hz), 8.08-8.13 (2H, m), 8.36 (1H, s), 8.44 (1H, s), 9.04 (1H, s), 9.96 (1H, s); ESIMS found for $C_{21}H_{26}N_6O$ m/z 379.2 (M+1).

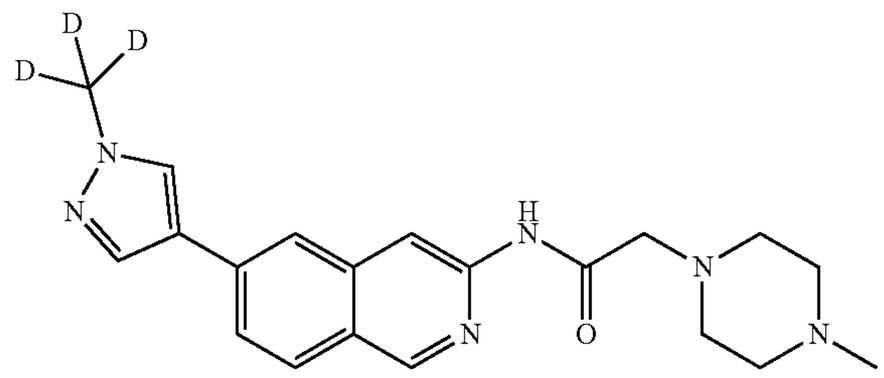
1013



N-(7-Chloro-6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)piperidine-4-carboxamide 1013

Off-white solid (200.0 mg, 0.541 mmol, 99.9% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.75-1.85 (2H, m), 1.93-1.99 (2H, m), 2.79-2.90 (3H, m), 3.28-3.34 (2H, m), 3.93 (3H, s), 7.98 (1H, s), 8.11 (1H, s), 8.26 (1H, s), 8.31 (1H, s), 8.47 (1H, s), 9.09 (1H, s), 10.71 (1H, s); ESIMS found for $C_{19}H_{20}ClN_5O$ m/z 370.1 (M+1).

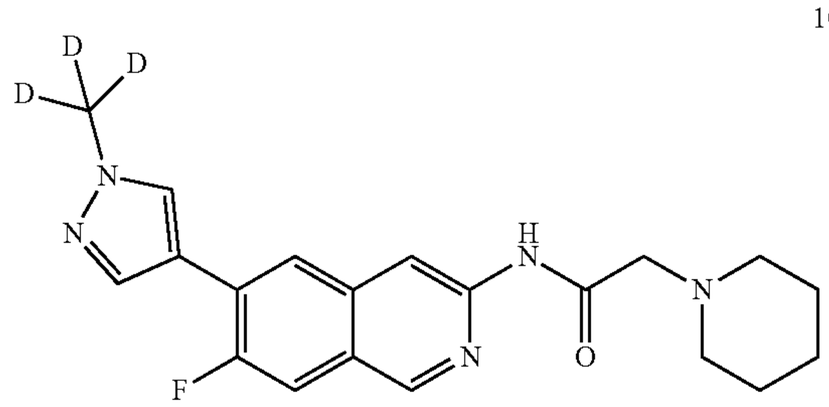
1014



N-(6-(1-(Methyl-d3)-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(4-methylpiperazin-1-yl)acetamide 1014

Light brown solid (92.0 mg, 0.250 mmol, 50.1% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 2.24 (3H, s), 2.46 (4H, br s), 2.60 (4H, br s), 3.23 (2H, s), 7.77 (1H, dd, J=8.51, 1.65 Hz), 8.02 (1H, d, J=8.51 Hz), 8.10 (2H, s), 8.36 (1H, s), 8.43 (1H, s), 9.04 (1H, s), 9.94 (1H, s); ESIMS found for $C_{20}H_{21}[^2H_3]N_6O$ m/z 368.2 (M+1).

1015

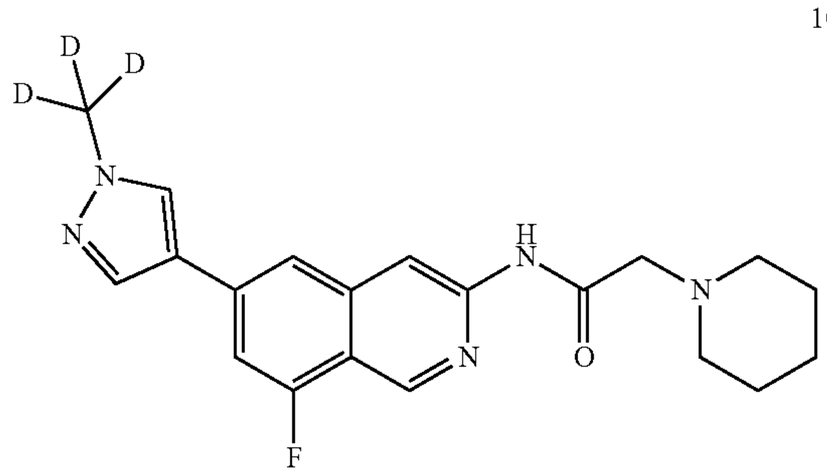


N-(7-Fluoro-6-(1-(methyl-d3)-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(piperidin-1-yl)acetamide 1015

Brown solid (20.0 mg, 0.054 mmol, 33.0% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.43 (2H, br d, J=5.21 Hz), 1.58 (4H, quin, J=5.56 Hz), 2.52 (4H, br s), 3.17 (2H,

s), 7.92 (1H, d, J=11.53 Hz), 8.13 (1H, s), 8.31 (1H, d, J=2.47 Hz), 8.33 (1H, d, J=7.68 Hz), 8.49 (1H, s), 9.05 (1H, s), 9.93 (1H, s); ESIMS found for $C_{20}H_{19}[^2H_3]FN_5O$ m/z 371.2 (M+1).

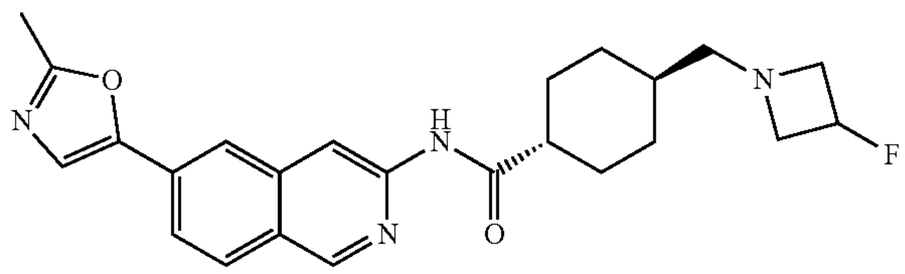
1016



N-(8-Fluoro-6-(1-(methyl-d3)-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(piperidin-1-yl)acetamide 1016

Pale yellow solid (46.0 mg, 0.124 mmol, 40.1% yield). ^1H NMR (499 MHz, DMSO-d_6) δ ppm 1.43 (2H, br d, J=4.94 Hz), 1.58 (4H, quin, J=5.56 Hz), 2.51-2.57 (4H, m), 3.19 (2H, s), 7.62 (1H, dd, J=12.08, 1.10 Hz), 7.99 (1H, s), 8.13 (1H, s), 8.40 (1H, d, J=0.82 Hz), 8.48 (1H, s), 9.16 (1H, s), 10.04 (1H, s); ESIMS found for $C_{20}H_{19}[^2H_3]FN_5O$ m/z 371.2 (M+1).

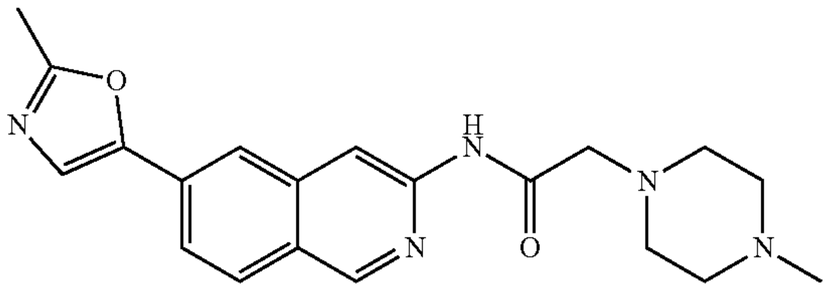
1018



trans-4-((3-Fluoroazetidin-1-yl)methyl)-N-(6-(2-methyloxazol-5-yl) isoquinolin-3-yl)cyclohexane-1-carboxamide 1018

Off-white solid (52.0 mg, 0.123 mmol, 51.7% yield). ^1H NMR (499 MHz, DMSO-d_6) δ ppm 0.91 (2H, qd, J=12.72, 3.02 Hz), 1.22-1.32 (1H, m), 1.44 (2H, qd, J=12.72, 3.29 Hz), 1.79 (2H, br dd, J=13.17, 2.47 Hz), 1.82-1.89 (2H, m), 2.29 (2H, d, J=6.59 Hz), 2.44-2.49 (1H, m), 2.53 (3H, s), 2.96-3.08 (2H, m), 3.49-3.59 (2H, m), 5.12 (1H, dq, J=58.00, 5.20 Hz), 7.78 (1H, s), 7.79-7.83 (1H, m), 8.06-8.12 (2H, m), 8.50 (1H, s), 9.10 (1H, s), 10.48 (1H, s); ESIMS found for $C_{24}H_{27}FN_4O_2$ m/z 423.2 (M+1).

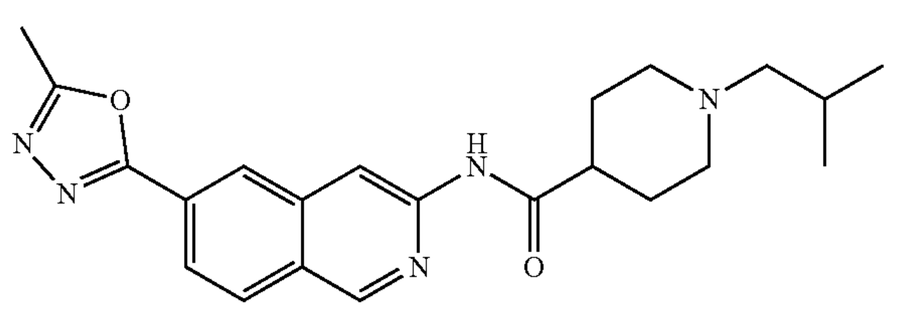
1019



N-(6-(2-Methyloxazol-5-yl)isoquinolin-3-yl)-2-(4-methylpiperazin-1-yl) acetamide 1019

Off-white solid (60.0 mg, 0.164 mmol, 49.8% yield). ^1H NMR (499 MHz, DMSO-d_6) δ ppm 2.19 (3H, s), 2.40 (4H, br s), 2.53 (3H, s), 2.58 (4H, br s), 3.23 (2H, s), 7.80 (1H, s), 7.83 (1H, dd, J=8.51, 1.65 Hz), 8.12 (1H, d, J=8.51 Hz), 8.16 (1H, s), 8.50 (1H, s), 9.12 (1H, s), 10.00 (1H, s); ESIMS found for $C_{20}H_{23}N_5O_2$ m/z 366.2 (M+1).

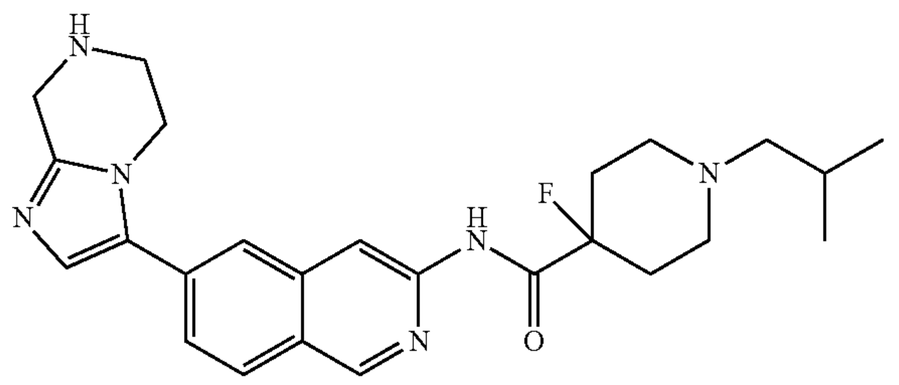
1020



1-Isobutyl-N-(6-(5-methyl-1,3,4-oxadiazol-2-yl) isoquinolin-3-yl)piperidine-4-carboxamide 1020

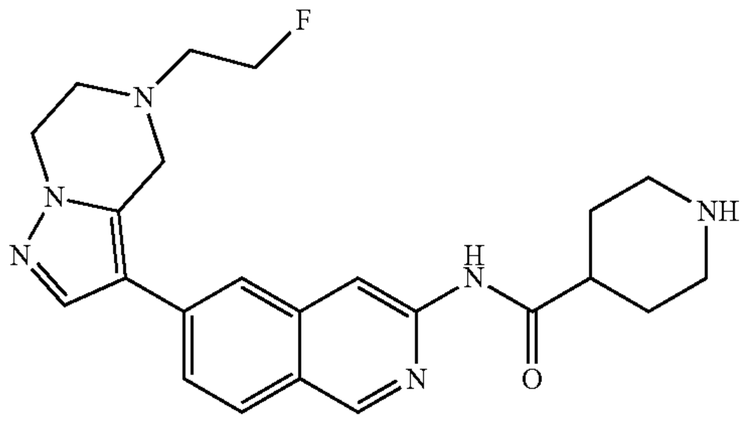
Off-white solid (40.0 mg, 0.102 mmol, 34.3% yield). ^1H NMR (499 MHz, DMSO-d_6) δ ppm 0.86 (6H, d, J=6.59 Hz), 1.62-1.73 (2H, m), 1.73-1.82 (3H, m), 1.83-1.92 (2H, m), 2.02 (2H, d, J=7.41 Hz), 2.52-2.59 (1H, m), 2.64 (3H, s), 2.87 (2H, br d, J=11.25 Hz), 8.04 (1H, dd, J=8.51, 1.37 Hz), 8.23 (1H, d, J=8.78 Hz), 8.47 (1H, s), 8.62 (1H, s), 9.24 (1H, s), 10.64 (1H, s); ESIMS found for $C_{22}H_{27}N_5O_2$ m/z 394.2 (M+1).

1021



4-Fluoro-1-isobutyl-N-(6-(5,6,7,8-tetrahydroimidazo [1,2-a]pyrazin-3-yl) isoquinolin-3-yl)piperidine-4-carboxamide 1021

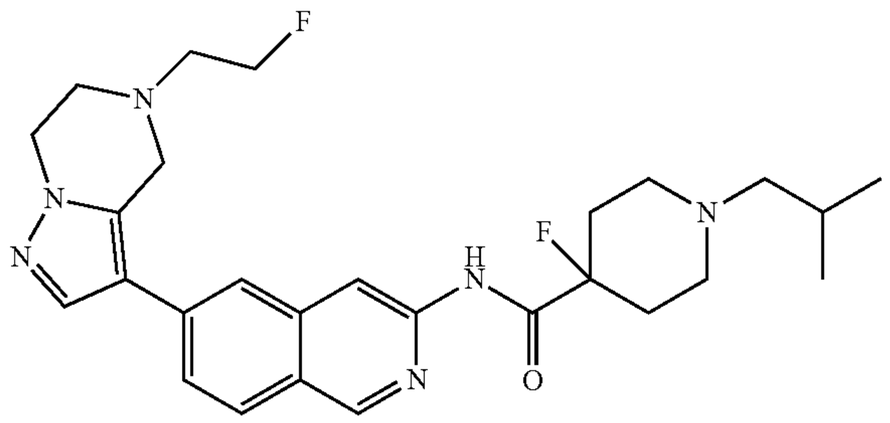
White solid (66.0 mg, 0.147 mmol, 47.5% yield). ^1H NMR (499 MHz, DMSO-d_6) δ ppm 0.88 (6H, d, J=6.59 Hz), 1.75-1.86 (1H, m), 1.91-2.01 (2H, m), 2.05-2.22 (4H, m), 2.09 (2H, d, J=7.41 Hz), 2.78 (2H, br d, J=7.68 Hz), 3.07 (2H, br t, J=5.21 Hz), 3.95 (2H, s), 4.12 (2H, t, J=5.21 Hz), 7.31 (1H, s), 7.72 (1H, dd, J=8.64, 1.51 Hz), 8.02 (1H, s), 8.11 (1H, d, J=8.51 Hz), 8.49 (1H, s), 9.15 (1H, s), 9.91 (1H, d, J=4.12 Hz); ESIMS found for $C_{25}H_{31}FN_6O$ m/z 451.25 (M+1).



N-(6-(5-(2-Fluoroethyl)-4,5,6,7-tetrahydropyrazolo [1,5-a]pyrazin-3-yl) isoquinolin-3-yl)piperidine-4-carboxamide 1022

White solid (14.0 mg, 0.033 mmol, 46.7% yield). ^{1}HNMR (499 MHz, DMSO-d_6) δ ppm 1.54 (2H, qd, J=12.12, 3.70 Hz), 1.70 (2H, br d, J=10.98 Hz), 2.47 (2H, br s), 2.64 (1H, tt, J=11.46, 3.50 Hz), 2.93-3.04 (4H, m), 3.07 (2H, br t, J=5.49 Hz), 4.08 (2H, s), 4.18 (2H, t, J=5.35 Hz), 4.66 (2H, dt, J=47.80, 4.70 Hz), 7.63 (1H, dd, J=8.51, 1.65 Hz), 7.75 (1H, s), 8.00 (1H, s), 8.02 (1H, d, J=8.78 Hz), 8.48 (1H, s), 9.05 (1H, s), 10.42 (1H, s); ESIMS found for $C_{23}H_{27}FN_6O$ m/z 423.2 (M+1).

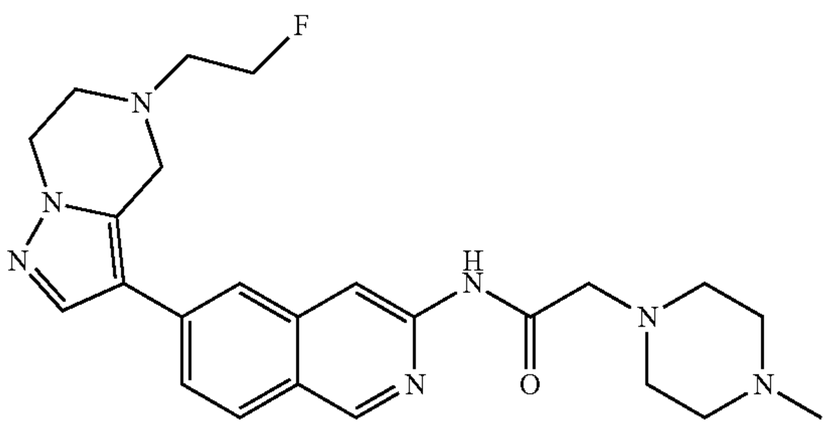
1023



4-Fluoro-N-(6-(5-(2-fluoroethyl)-4,5,6,7-tetrahydro-pyrazolo[1,5-a]pyrazin-3-yl)isoquinolin-3-yl)-1-isobutylpiperidine-4-carboxamide 1023

White amorphous solid (48.8 mg, 0.098 mmol, 88.2% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 0.88 (6H, d, J=6.59 Hz), 1.79 (1H, dt, J=13.52, 6.83 Hz), 1.95 (2H, br t, J=11.66 Hz), 2.06-2.22 (4H, m), 2.09 (2H, d, J=7.68 Hz), 2.78 (2H, br d, J=7.96 Hz), 2.99 (2H, dt, J=28.60, 4.95 Hz), 3.08 (2H, t, J=5.49 Hz), 4.09 (2H, s), 4.18 (2H, t, J=5.49 Hz), 4.66 (2H, dt, J=47.85, 4.95 Hz), 7.70 (1H, dd, J=8.51, 1.65 Hz), 7.84 (1H, s), 8.01 (1H, s), 8.08 (1H, d, J=8.78 Hz), 8.45 (1H, s), 9.11 (1H, s), 9.86 (1H, d, J=4.39 Hz); ESIMS found for $C_{27}H_{34}F_2N_6O$ m/z 497.3 (M+1).

1024

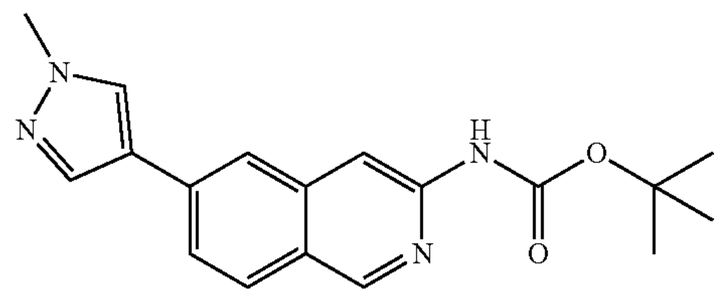


1022

N-(6-(5-(2-Fluoroethyl)-4,5,6,7-tetrahydropyrazolo [1,5-a]pyrazin-3-yl) isoquinolin-3-yl)-2-(4-methyl-piperazin-1-yl)acetamide 1024

Orange solid (3.0 mg, 0.007 mmol, 4.5% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 2.19 (3H, s), 2.40 (4H, br s), 2.58 (4H, br s), 2.99 (2H, dt, J=28.60, 4.95 Hz), 3.07 (2H, t, J=5.49 Hz), 3.22 (2H, s), 4.09 (2H, s), 4.18 (2H, t, J=5.35 Hz), 4.66 (2H, dt, J=47.80, 4.95 Hz), 7.66 (1H, dd, J=8.51, 1.65 Hz), 7.82 (1H, s), 8.01 (1H, s), 8.05 (1H, d, J=8.51 Hz), 8.47 (1H, s), 9.07 (1H, s), 9.94 (1H, s); ESIMS found for $C_{24}H_{30}FN_7O$ m/z 452.2 (M+1).

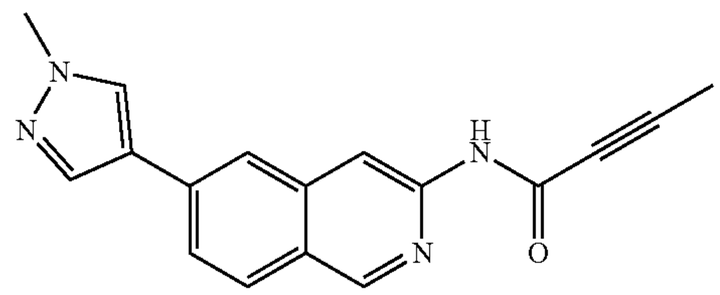
1025



tert-Butyl (6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)carbamate 1025

White solid (96.0 mg, 0.296 mmol, 28.1% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.51 (9H, s), 3.90 (3H, s), 7.71 (1H, dd, J=8.51, 1.65 Hz), 7.97 (1H, d, J=8.51 Hz), 8.04 (1H, s), 8.07 (1H, s), 8.10 (1H, s), 8.33 (1H, s), 8.97 (1H, s), 9.78 (1H, s); ESIMS found for $C_{18}H_{20}N_4O_2$ m/z 325.2 (M+1).

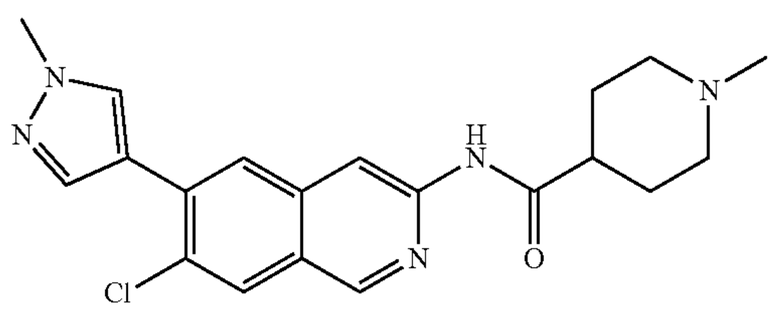
1026



N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl) but-2-ynamide 1026

Yellow solid (3.7 mg, 0.013 mmol, 2.8% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 2.05 (3H, s), 3.90 (3H, s), 7.78 (1H, dd, J=8.78, 1.65 Hz), 8.01 (1H, d, J=8.78 Hz), 8.08 (1H, s), 8.09 (1H, s), 8.34 (2H, s), 9.03 (1H, s), 11.06 (1H, br s); ESIMS found for $C_{17}H_{14}N_4O$ m/z 290.9 (M+1).

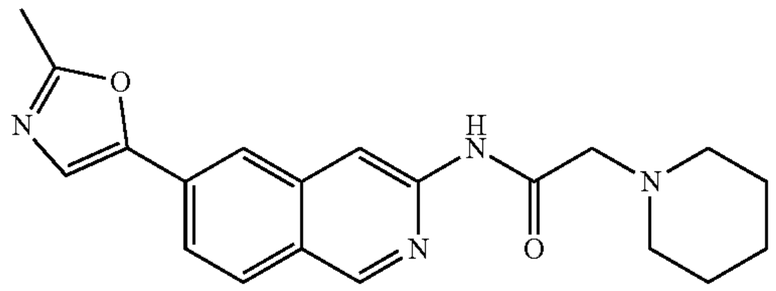
1027



N-(7-Chloro-6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-1-methylpiperidine-4-carboxamide 1027

White solid (2.0 mg, 0.005 mmol, 1.3% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.61-1.72 (2H, m), 1.73-1.80 (2H, m), 1.83-1.90 (2H, m), 2.16 (3H, s), 2.45-2.49 (1H, m), 2.81 (2H, br d, J=11.25 Hz), 3.93 (3H, s), 7.97 (1H, s), 8.09 (1H, s), 8.25 (1H, s), 8.30 (1H, s), 8.48 (1H, s), 9.08 (1H, s), 10.56 (1H, s); ESIMS found for $C_{20}H_{22}ClN_5O$ m/z 384.2 (M+1).

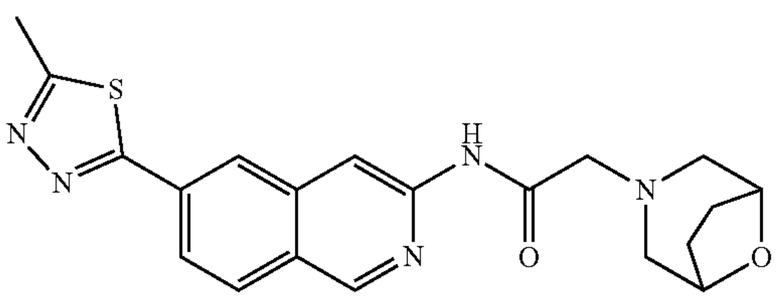
1028



N-(6-(2-Methyloxazol-5-yl)isoquinolin-3-yl)-2-(piperidin-1-yl)acetamide 1028

Off-white solid (57.0 mg, 0.163 mmol, 32.5% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.43 (2H, br d, J=5.21 Hz), 1.58 (4H, quin, J=5.56 Hz), 2.52 (4H, br s), 2.53 (3H, s), 3.18 (2H, s), 7.80 (1H, s), 7.83 (1H, dd, J=8.51, 1.65 Hz), 8.12 (1H, d, J=8.78 Hz), 8.16 (1H, s), 8.50 (1H, s), 9.12 (1H, s), 9.98 (1H, s); ESIMS found for $C_{20}H_{22}N_4O_2$ m/z 351.15 (M+1).

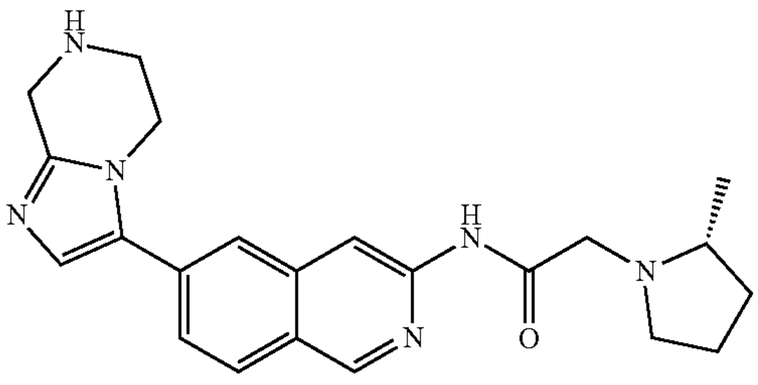
1029



2-(8-Oxa-3-azabicyclo[3.2.1]octan-3-yl)-N-(6-(5-methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)acetamide 1029

Beige solid (200.0 mg, 0.506 mmol, 56.0% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.80-1.88 (2H, m), 2.00-2.06 (2H, m), 2.48 (2H, br s), 2.67 (2H, br d, J=10.98 Hz), 2.83 (3H, s), 3.20 (2H, s), 4.27 (2H, br d, J=1.92 Hz), 8.12 (1H, dd, J=8.51, 1.65 Hz), 8.20 (1H, d, J=8.78 Hz), 8.51 (1H, s), 8.61 (1H, s), 9.24 (1H, s), 10.09 (1H, s); ESIMS found for $C_{20}H_{21}N_5O_2S$ m/z 396.15 (M+1).

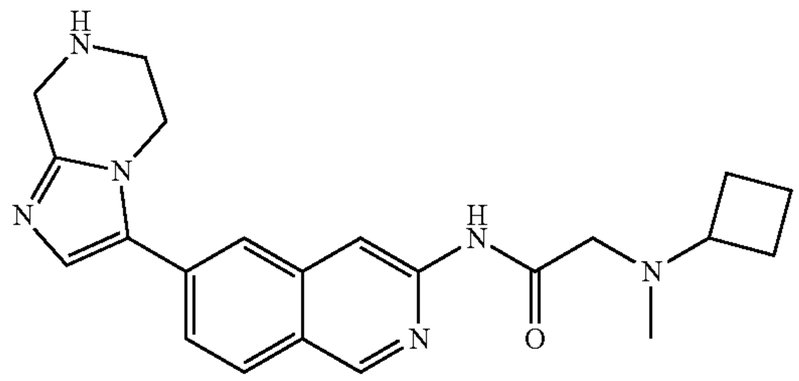
1030



(R)-2-(2-Methylpyrrolidin-1-yl)-N-(6-(5,6,7,8-tetrahydroimidazo[1,2-a] pyrazin-3-yl)isoquinolin-3-yl) acetamide 1030

White solid (25.2 mg, 0.065 mmol, 36.0% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.09 (3H, d, J=6.04 Hz), 1.42 (1H, dddd, J=12.18, 10.26, 8.30, 6.59 Hz), 1.67-1.85 (2H, m), 1.90-2.02 (1H, m), 2.41 (1H, q, J=8.51 Hz), 2.57-2.67 (1H, m), 3.08 (2H, br t, J=5.21 Hz), 3.13-3.20 (2H, m), 3.54 (1H, d, J=16.19 Hz), 3.95 (2H, s), 4.12 (2H, t, J=5.21 Hz), 7.30 (1H, s), 7.68 (1H, dd, J=8.51, 1.65 Hz), 7.99 (1H, s), 8.08 (1H, d, J=8.51 Hz), 8.51 (1H, s), 9.10 (1H, s), 9.93 (1H, s); ESIMS found for $C_{22}H_{26}N_6O$ m/z 391.2 (M+1).

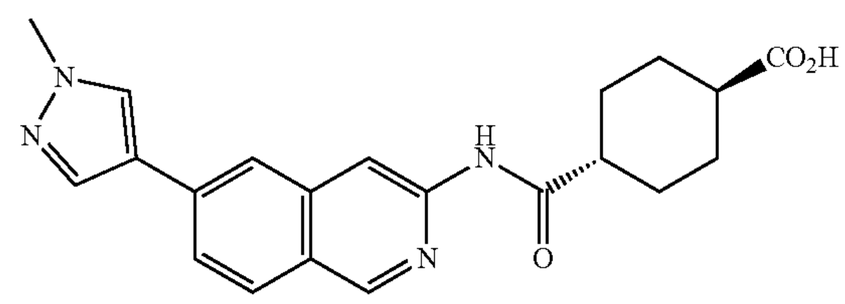
1031



2-(Cyclobutyl(methyl)amino)-N-(6-(5,6,7,8-tetrahydroimidazo[1,2-a] pyrazin-3-yl)isoquinolin-3-yl) acetamide 1031

Light olive-colored gum (43.2 mg, 0.111 mmol, 46.4% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.54-1.71 (2H, m), 1.80-1.93 (2H, m), 1.96-2.07 (2H, m), 2.23 (3H, s), 3.12 (1H, br d, J=14.27 Hz), 3.06-3.09 (2H, m), 3.12 (2H, s), 3.95 (2H, s), 4.12 (2H, t, J=5.21 Hz), 7.30 (1H, s), 7.68 (1H, dd, J=8.51, 1.65 Hz), 7.99 (1H, s), 8.08 (1H, d, J=8.51 Hz), 8.51 (1H, s), 9.11 (1H, s), 9.96 (1H, s); ESIMS found for $C_{22}H_{26}N_6O$ m/z 391.2 (M+1).

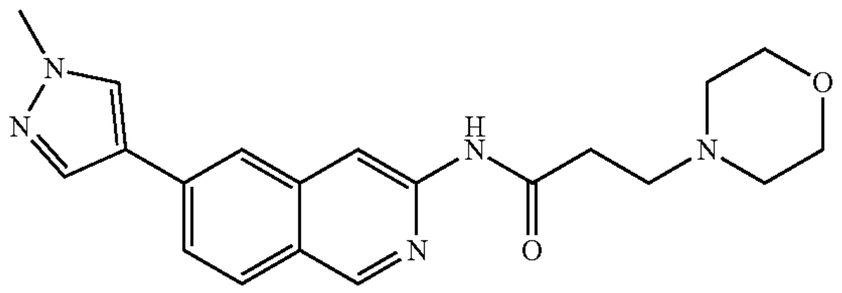
1032



trans-4-((6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)carbamoyl) cyclohexane-1-carboxylic acid 1032

Beige solid (135.0 mg, 0.357 mmol, 70.0% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.29-1.40 (2H, m), 1.49 (2H, qd, J=12.76, 3.16 Hz), 1.85-1.94 (2H, m), 1.97 (2H, br dd, J=13.45, 2.74 Hz), 2.22 (1H, tt, J=12.18, 3.60 Hz), 2.51-2.58 (1H, m), 3.90 (3H, s), 7.74 (1H, dd, J=8.51, 1.65 Hz), 8.00 (1H, d, J=8.51 Hz), 8.03 (1H, s), 8.08 (1H, s), 8.35 (1H, s), 8.42 (1H, s), 9.02 (1H, s), 10.43 (1H, s), 12.07 (1H, br s); ESIMS found for $C_{21}H_{22}N_4O_3$ m/z 379.1 (M+1).

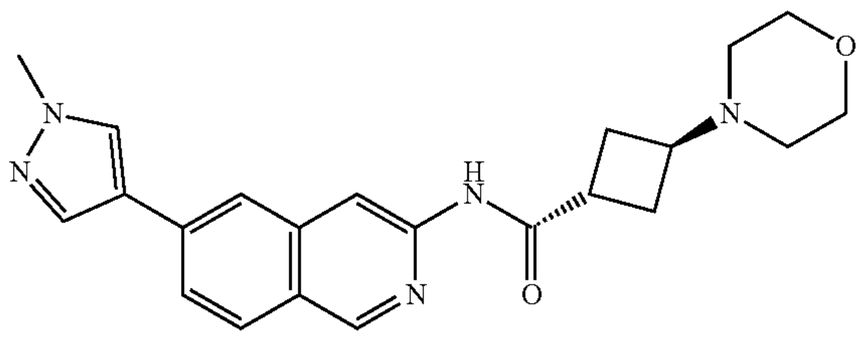
1034



N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-3-morpholinopropanamide 1034

White solid (12.0 mg, 0.033 mmol, 12.0% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 2.44 (4H, br s), 2.57-2.63 (2H, m), 2.63-2.70 (2H, m), 3.59 (4H, t, J=4.67 Hz), 3.90 (3H, s), 7.75 (1H, dd, J=8.51, 1.65 Hz), 8.00 (1H, d, J=8.51 Hz), 8.06 (1H, s), 8.09 (1H, s), 8.36 (1H, s), 8.44 (1H, s), 9.03 (1H, s), 10.74 (1H, s); ESIMS found for $C_{20}H_{23}N_5O_2$ m/z 366.2 (M+1).

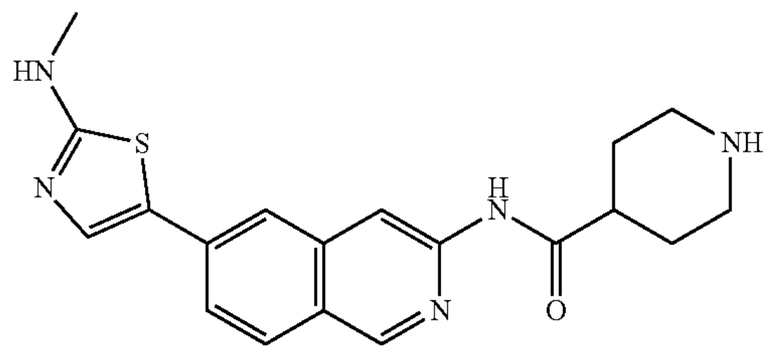
1035



trans-N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-3-morpholinocyclobutane-1-carboxamide 1035

White solid (18.0 mg, 0.075 mmol, 23.92% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 2.07-2.16 (2H, m), 2.22-2.32 (6H, m), 2.85-2.95 (1H, m), 3.22-3.30 (1H, m), 3.59 (4H, t, J=4.39 Hz), 3.91 (3H, s), 7.74 (1H, dd, J=8.51, 1.65 Hz), 8.00 (1H, d, J=8.51 Hz), 8.04 (1H, s), 8.08 (1H, s), 8.35 (1H, s), 8.47 (1H, s), 9.01 (1H, s), 10.41 (1H, s); ESIMS found for $C_{22}H_{25}N_5O_2$ m/z 392. (M+1).

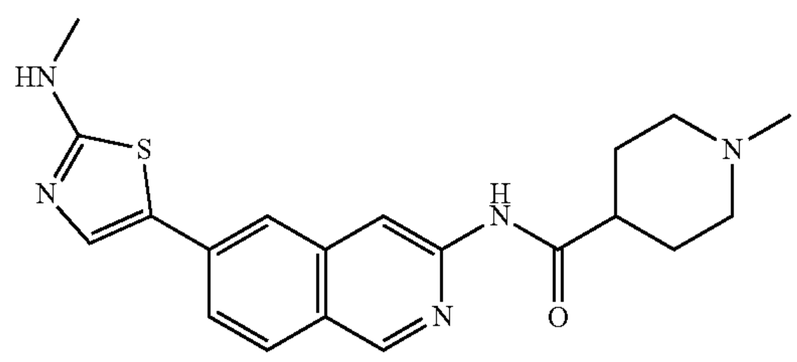
1040



N-(6-(2-(Methylamino)thiazol-5-yl)isoquinolin-3-yl)piperidine-4-carboxamide 1040

Beige solid (80.0 mg, 0.218 mmol, 91.1% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.46-1.60 (2H, m), 1.66-1.74 (2H, m), 2.43-2.49 (2H, m), 2.59-2.68 (1H, m), 2.89 (3H, d, J=4.94 Hz), 2.93-3.01 (2H, m), 7.69 (1H, s), 7.70-7.74 (1H, m), 7.78 (1H, s), 7.90-7.98 (2H, m), 8.40 (1H, s), 8.99 (1H, s), 10.40 (1H, s); ESIMS found for $C_{19}H_{21}N_5OS$ m/z 368.15 (M+1).

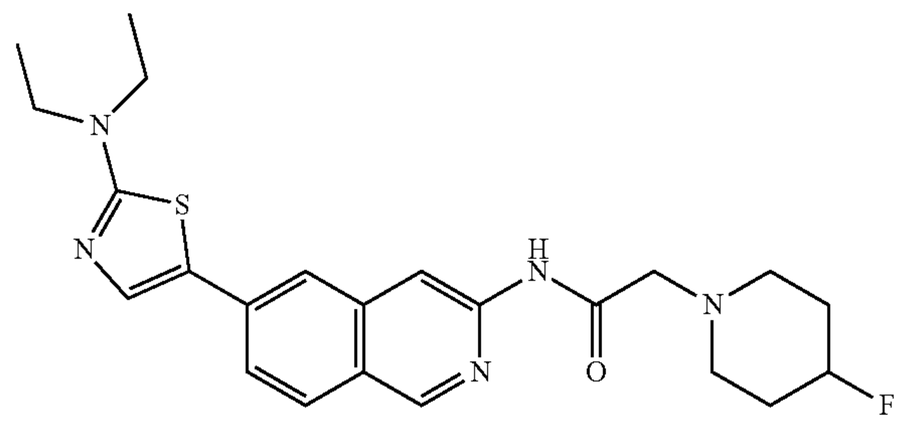
1041



1-Methyl-N-(6-(2-(methylamino)thiazol-5-yl)isoquinolin-3-yl)piperidine-4-carboxamide 1041

Yellow solid (32.0 mg, 0.084 mmol, 77.1% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.60-1.72 (2H, m), 1.73-1.80 (2H, m), 1.86 (2H, td, J=11.60, 2.06 Hz), 2.16 (3H, s), 2.44-2.49 (1H, m), 2.77-2.85 (2H, m), 2.89 (3H, d, J=4.94 Hz), 7.69 (1H, s), 7.72 (1H, dd, J=8.64, 1.78 Hz), 7.77 (1H, s), 7.89-7.97 (2H, m), 8.40 (1H, s), 8.99 (1H, s), 10.45 (1H, s); ESIMS found for $C_{20}H_{23}N_5OS$ m/z 382.2 (M+1).

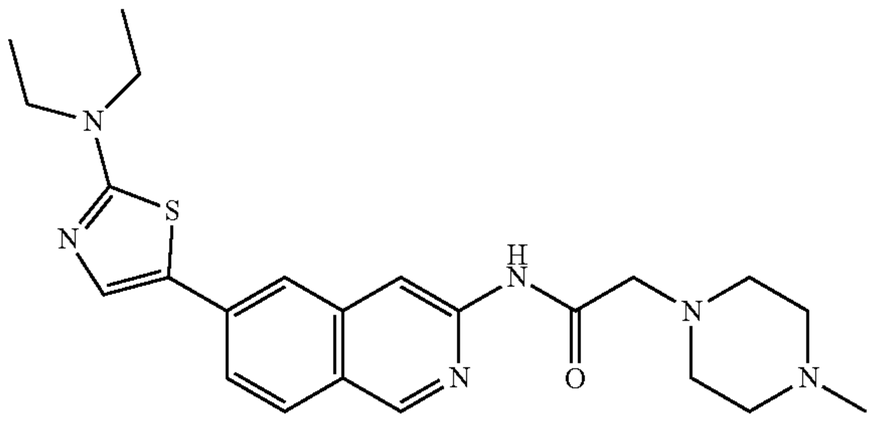
1047



N-(6-(2-(Diethylamino)thiazol-5-yl)isoquinolin-3-yl)-2-(4-fluoropiperidin-1-yl)acetamide 1047

Yellow solid (22.0 mg, 0.050 mmol, 26.7% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.21 (6H, t, J=7.14 Hz), 1.73-1.85 (2H, m), 1.86-1.99 (2H, m), 2.52-2.58 (2H, m), 2.66-2.75 (2H, m), 3.24 (2H, s), 3.52 (4H, q, J=7.14 Hz), 4.66-4.83 (1H, m), 7.74 (1H, dd, J=8.51, 1.65 Hz), 7.79 (1H, s), 7.86 (1H, s), 7.98 (1H, d, J=8.51 Hz), 8.40 (1H, s), 9.01 (1H, s), 9.97 (1H, s); ESIMS found for $C_{23}H_{28}FN_5OS$ m/z 442.2 (M+1).

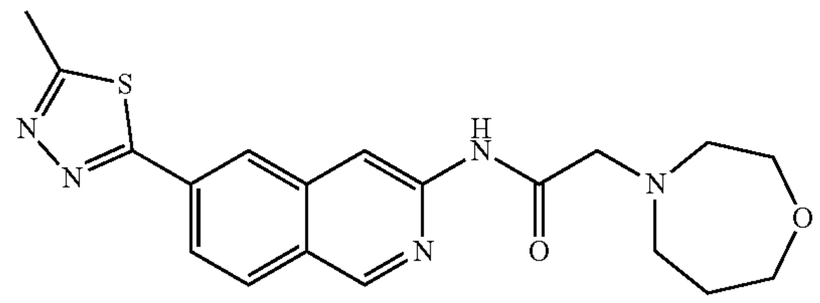
1048



N-(6-(2-(Diethylamino)thiazol-5-yl)isoquinolin-3-yl)-2-(4-methylpiperazin-1-yl)acetamide 1048

Beige solid (25.0 mg, 0.057 mmol, 30.5% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.21 (6H, t, J=7.00 Hz), 2.19 (3H, s), 2.40 (4H, br s), 2.58 (4H, br s), 3.21 (2H, s), 3.52 (4H, q, J=7.14 Hz), 7.74 (1H, dd, J=8.64, 1.78 Hz), 7.79 (1H, s), 7.86 (1H, s), 7.98 (1H, d, J=8.51 Hz), 8.39 (1H, s), 9.01 (1H, s), 9.92 (1H, s); ESIMS found for $C_{23}H_{30}N_6OS$ m/z 439.2 (M+1).

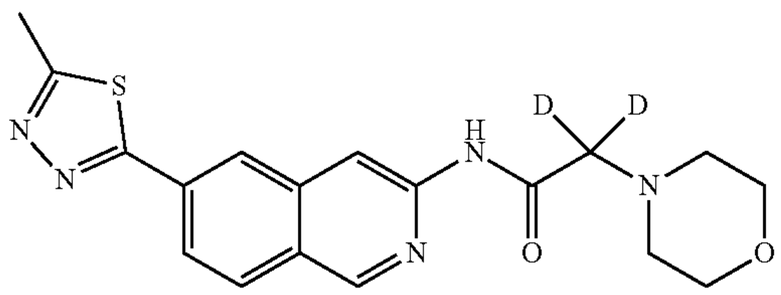
1049



N-(6-(5-Methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)-2-(1,4-oxazepan-4-yl) acetamide 1049

Beige solid (74.0 mg, 0.193 mmol, 35.1% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.87 (2H, quin, J=5.83 Hz), 2.83 (3H, s), 2.83-2.86 (4H, m), 3.43 (2H, s), 3.66-3.70 (2H, m), 3.74 (2H, t, J=6.04 Hz), 8.12 (1H, dd, J=8.51, 1.65 Hz), 8.21 (1H, d, J=8.51 Hz), 8.51 (1H, d, J=0.82 Hz), 8.62 (1H, s), 9.23 (1H, s), 10.15 (1H, s); ESIMS found for $C_{19}H_{21}N_5O_2S$ m/z 384.15 (M+1).

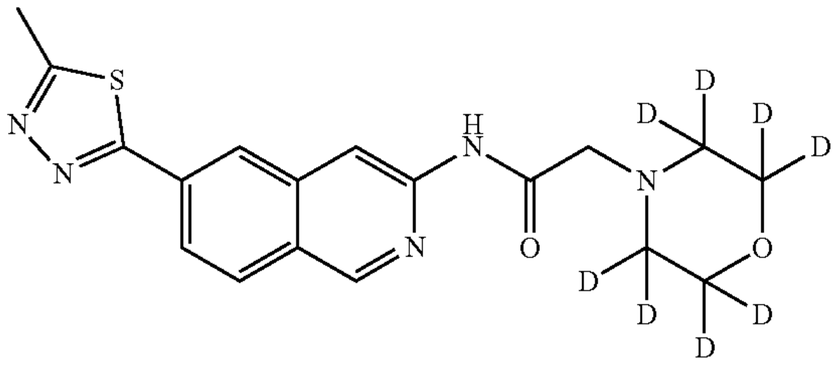
1051



N-(6-(5-Methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)-2-morpholinoacetamide-2,2-d_2 1051

White solid (20.0 mg, 0.054 mmol, 32.5% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 2.55-2.61 (4H, m), 2.83 (3H, s), 3.62-3.69 (4H, m), 8.12 (1H, dd, J=8.64, 1.78 Hz), 8.21 (1H, d, J=8.51 Hz), 8.51 (1H, s), 8.62 (1H, s), 9.23 (1H, s), 10.18 (1H, d, J=3.02 Hz); ESIMS found for $C_{18}H_{17}[^2H_2]N_5O_2S$ m/z 372.1 (M+1).

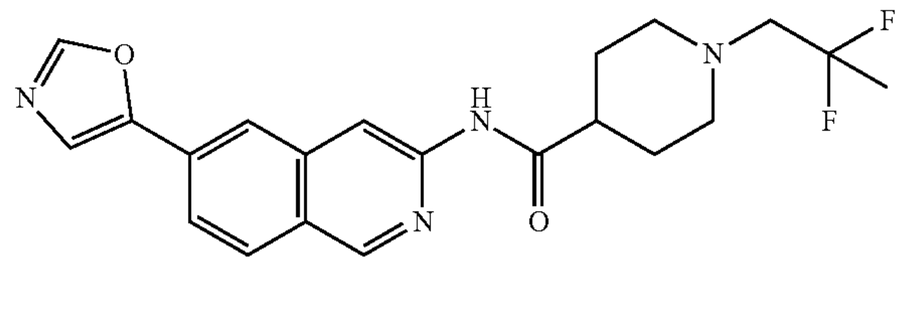
1052



N-(6-(5-Methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)-2-(morpholino-d_8) acetamide 1052

Off-white solid (22.0 mg, 0.058 mmol, 7.2% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 2.83 (3H, s), 3.26 (2H, s), 8.12 (1H, dd, J=8.51, 1.65 Hz), 8.21 (1H, d, J=8.51 Hz), 8.51 (1H, s), 8.62 (1H, s), 9.23 (1H, s), 10.17 (1H, s); ESIMS found for $C_{18}H_{11}[^2H_8]N_5O_2S$ m/z 378.2 (M+1).

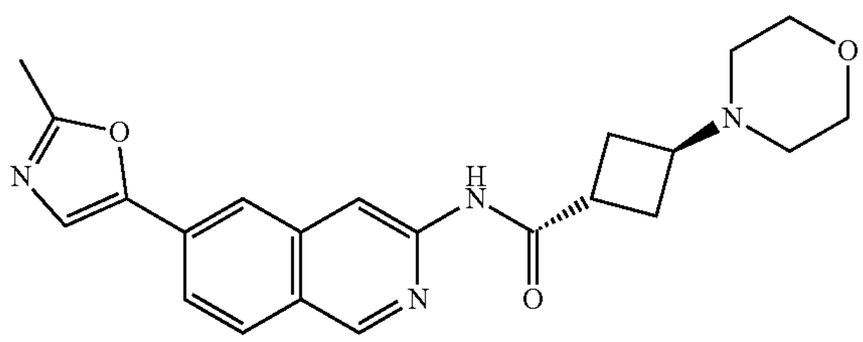
1057



1-(2,2-Difluoropropyl)-N-(6-(oxazol-5-yl)isoquinolin-3-yl)piperidine-4-carboxamide 1057

White solid (22.5 mg, 0.056 mmol, 22.8% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.63 (3H, t, J=19.07 Hz), 1.67-1.74 (2H, m), 1.75-1.81 (2H, m), 2.22 (2H, td, J=11.60, 2.06 Hz), 2.52-2.60 (1H, m), 2.71 (2H, t, J=14.13 Hz), 2.95 (2H, br d, J=11.53 Hz), 7.87 (1H, dd, J=8.51, 1.65 Hz), 7.95 (1H, s), 8.13 (1H, d, J=8.51 Hz), 8.20 (1H, s), 8.54 (1H, s), 8.58 (1H, s), 9.13 (1H, s), 10.58 (1H, s); ESIMS found for $C_{21}H_{22}F_2N_4O_2$ m/z 401.2 (M+1).

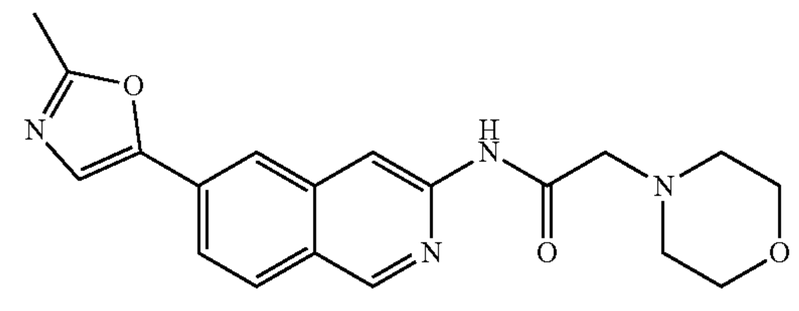
1061



trans-N-(6-(2-Methyloxazol-5-yl)isoquinolin-3-yl)-3-morpholinocyclobutane-1-carboxamide 1061

Grey solid (15.0 mg, 0.038 mmol, 19.9% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 2.07-2.16 (2H, m), 2.22-2.32 (6H, m), 2.54 (3H, s), 2.90 (1H, quin, J=7.14 Hz), 3.23-3.30 (1H, m), 3.59 (4H, t, J=4.39 Hz), 7.79 (1H, s), 7.80-7.83 (1H, m), 8.07-8.13 (2H, m), 8.54 (1H, s), 9.10 (1H, s), 10.50 (1H, s); ESIMS found for $C_{22}H_{24}N_4O_3$ m/z 393.2 (M+1).

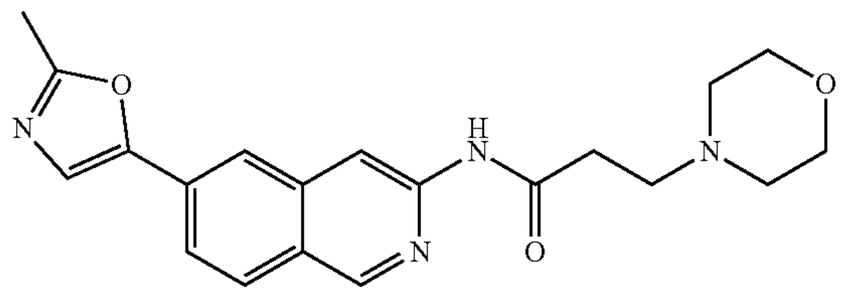
1067



N-(6-(2-Methyloxazol-5-yl)isoquinolin-3-yl)-2-morpholinoacetamide 1067

Off-white solid (41.0 mg, 0.116 mmol, 40.7% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 2.53 (3H, s), 2.55-2.60 (4H, m), 3.25 (2H, s), 3.62-3.69 (4H, m), 7.80 (1H, s), 7.83 (1H, dd, J=8.51, 1.65 Hz), 8.12 (1H, d, J=8.78 Hz), 8.16 (1H, s), 8.51 (1H, s), 9.12 (1H, s), 10.08 (1H, s); ESIMS found for $C_{19}H_{20}N_4O_3$ m/z 353.15 (M+1).

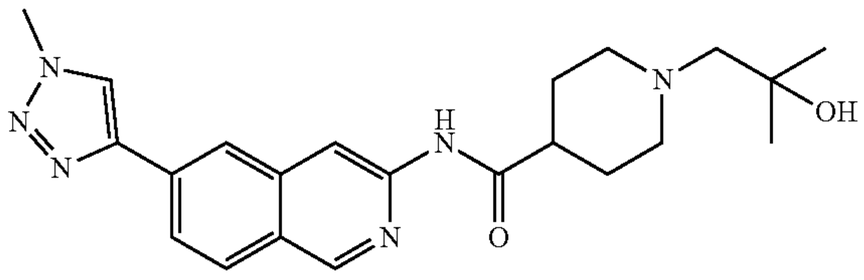
1068



N-(6-(2-Methyloxazol-5-yl)isoquinolin-3-yl)-3-morpholinopropanamide 1068

Beige solid (21.0 mg, 0.057 mmol, 20.9% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 2.44 (4H, br s), 2.53 (3H, s), 2.57-2.64 (2H, m), 2.64-2.71 (2H, m), 3.59 (4H, t, J=4.53 Hz), 7.79 (1H, s), 7.81 (1H, dd, J=8.51, 1.65 Hz), 8.10 (1H, d, J=8.51 Hz), 8.12 (1H, s), 8.50 (1H, s), 9.11 (1H, s), 10.82 (1H, s); ESIMS found for $C_{20}H_{22}N_4O_3$ m/z 367.15 (M+1).

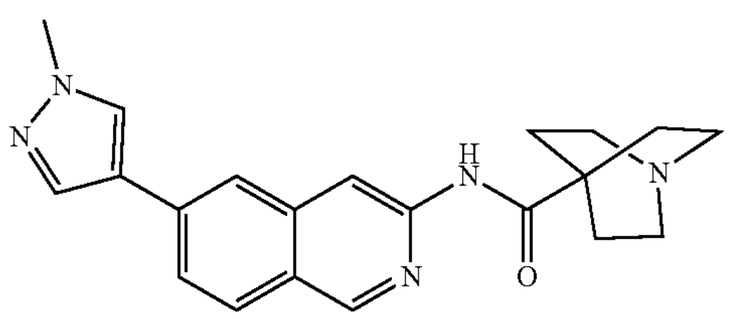
1070



1-(2-Hydroxy-2-methylpropyl)-N-(6-(1-methyl-1H-1,2,3-triazol-4-yl) isoquinolin-3-yl)piperidine-4-carboxamide 1070

White solid (26.0 mg, 0.064 mmol, 22.5% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 0.86 (6H, d, J=6.59 Hz), 1.62-1.73 (2H, m), 1.74-1.81 (2H, m), 1.83-1.92 (2H, m), 2.02 (2H, d, J=7.41 Hz), 2.52-2.59 (1H, m), 2.87 (2H, br d, J=11.53 Hz), 4.09 (1H, s), 4.14 (3H, s), 8.01 (1H, dd, J=8.51, 1.37 Hz), 8.11 (1H, d, J=8.51 Hz), 8.28 (1H, s), 8.51 (1H, s), 8.73 (1H, s), 9.11 (1H, s), 10.52 (1H, s); ESIMS found for $C_{22}H_{28}N_6O_2$ m/z 409.2 (M+1).

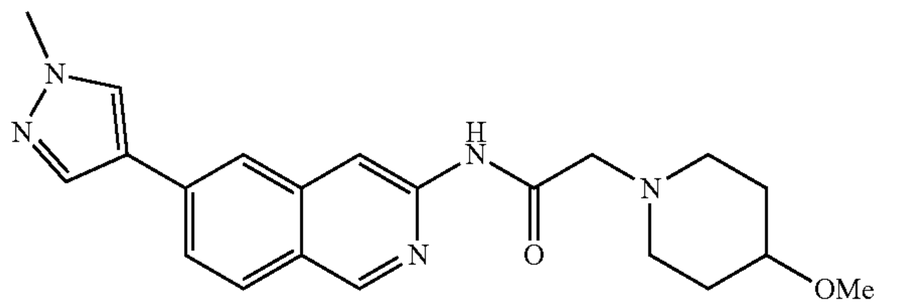
1071



N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl) quinuclidine-4-carboxamide 1071

Beige solid (27.0 mg, 0.075 mmol, 53.8% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.72-1.81 (6H, m), 2.74-2.83 (6H, m), 3.90 (3H, s), 7.75 (1H, dd, J=8.51, 1.65 Hz), 8.01 (1H, d, J=8.51 Hz), 8.04 (1H, s), 8.07 (1H, d, J=0.82 Hz), 8.35 (1H, s), 8.41 (1H, s), 9.04 (1H, s), 9.59 (1H, s); ESIMS found for $C_{21}H_{23}N_5O$ m/z 362.2 (M+1).

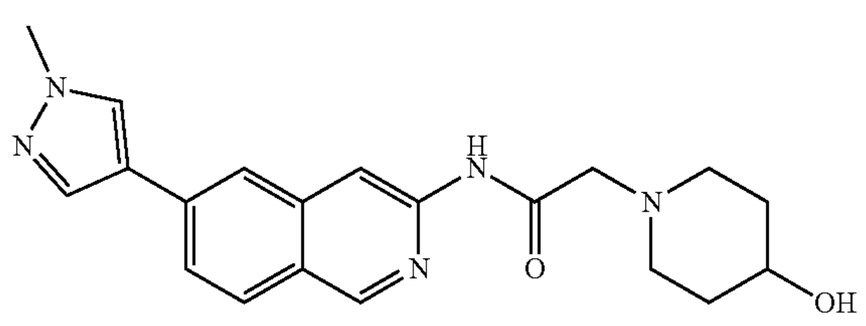
1077



2-(4-Methoxypiperidin-1-yl)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)acetamide 1077

Off-white solid (79.0 mg, 0.208 mmol, 41.6% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.48-1.57 (2H, m), 1.83-1.93 (2H, m), 2.32-2.41 (2H, m), 2.73-2.82 (2H, m), 3.18-3.27 (1H, m), 3.20 (2H, s), 3.24 (3H, s), 3.90 (3H, s), 7.77 (1H, dd, J=8.51, 1.65 Hz), 8.02 (1H, d, J=8.78 Hz), 8.10 (2H, s), 8.37 (1H, s), 8.43 (1H, s), 9.04 (1H, s), 9.94 (1H, s); ESIMS found for $C_{21}H_{25}N_5O_2$ m/z 380.2 (M+1).

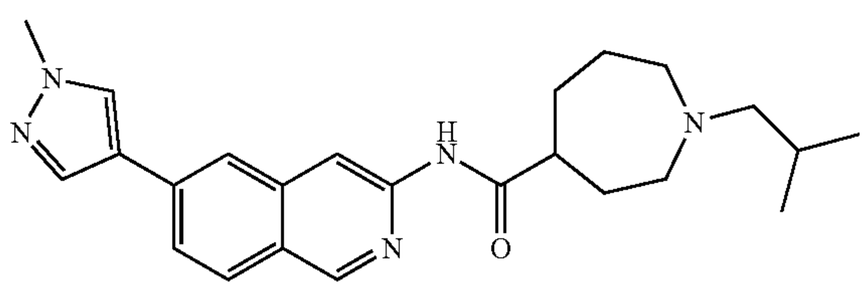
1078



2-(4-Hydroxypiperidin-1-yl)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)acetamide 1078

Off-white solid (84.0 mg, 0.230 mmol, 46.0% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.49 (2H, dtd, J=12.66, 9.52, 9.52, 3.70 Hz), 1.73-1.82 (2H, m), 2.28-2.35 (2H, m), 2.76-2.83 (2H, m), 3.19 (2H, s), 3.47-3.56 (1H, m), 3.90 (3H, s), 4.60 (1H, d, J=4.12 Hz), 7.77 (1H, dd, J=8.51, 1.65 Hz), 8.02 (1H, d, J=8.51 Hz), 8.10 (2H, s), 8.37 (1H, s), 8.43 (1H, s), 9.04 (1H, s), 9.93 (1H, s); ESIMS found for $C_{20}H_{23}N_5O_2$ m/z 366.2 (M+1).

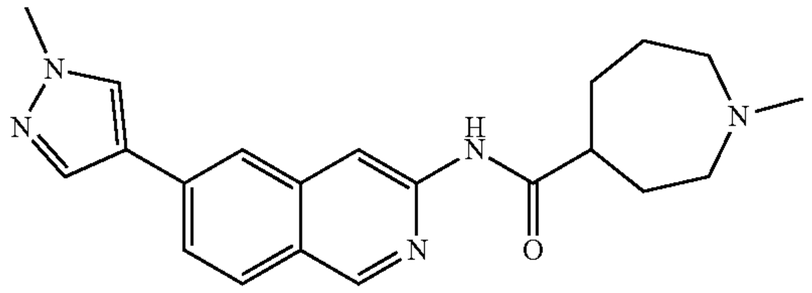
1079



1-Isobutyl-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)azepane-4-carboxamide 1079

Beige solid (12.0 mg, 0.030 mmol, 14.8% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 0.86 (3H, d, J=2.20 Hz), 0.88 (3H, d, J=2.20 Hz), 1.53-1.62 (1H, m), 1.64-1.82 (4H, m), 1.82-1.93 (2H, m), 2.13-2.25 (2H, m), 2.54-2.62 (3H, m), 2.66-2.74 (1H, m), 2.80-2.89 (1H, m), 3.90 (3H, s), 7.74 (1H, dd, J=8.51, 1.37 Hz), 7.99 (1H, d, J=8.51 Hz), 8.02 (1H, s), 8.07 (1H, s), 8.35 (1H, s), 8.42 (1H, s), 9.02 (1H, s), 10.42 (1H, s); ESIMS found for $C_{24}H_{31}N_5O$ m/z 406.25 (M+1).

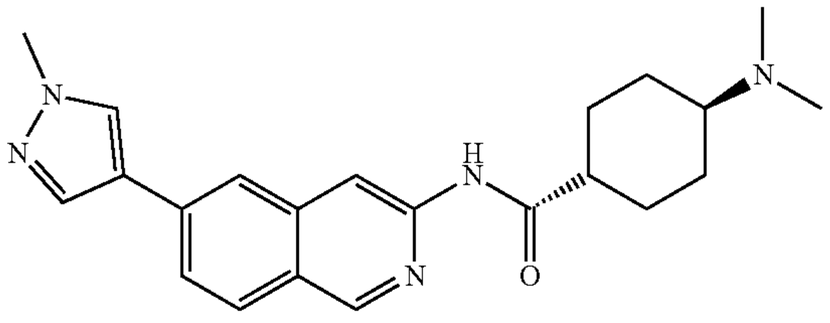
1080



1-Methyl-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)azepane-4-carboxamide 1080

White solid (11.0 mg, 0.030 mmol, 15.1% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.56-1.66 (1H, m), 1.71-1.82 (2H, m), 1.82-1.93 (3H, m), 2.27 (3H, s), 2.45-2.58 (3H, m), 2.62-2.72 (1H, m), 2.81-2.90 (1H, m), 3.90 (3H, s), 7.74 (1H, dd, J=8.37, 1.51 Hz), 7.99 (1H, d, J=8.51 Hz), 8.03 (1H, s), 8.08 (1H, s), 8.35 (1H, s), 8.42 (1H, s), 9.02 (1H, s), 10.43 (1H, s); ESIMS found for $C_{21}H_{25}N_5O$ m/z 364.2 (M+1).

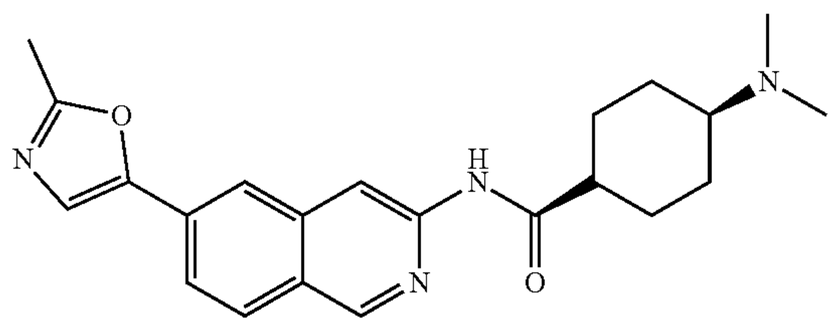
1081



trans-4-(Dimethylamino)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)cyclohexane-1-carboxamide 1081

Beige solid (5.0 mg, 0.013 mmol, 7.7% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.13-1.22 (2H, m), 1.43-1.54 (2H, m), 1.84-1.96 (4H, m), 2.11-2.20 (1H, m), 2.18 (6H, s), 2.42-2.49 (1H, m), 3.90 (3H, s), 7.74 (1H, dd, J=8.51, 1.65 Hz), 7.99 (1H, d, J=8.51 Hz), 8.02 (1H, s), 8.07 (1H, d, J=0.82 Hz), 8.35 (1H, s), 8.42 (1H, s), 9.02 (1H, s), 10.41 (1H, s); ESIMS found for $C_{22}H_{27}N_5O$ m/z 378.2 (M+1).

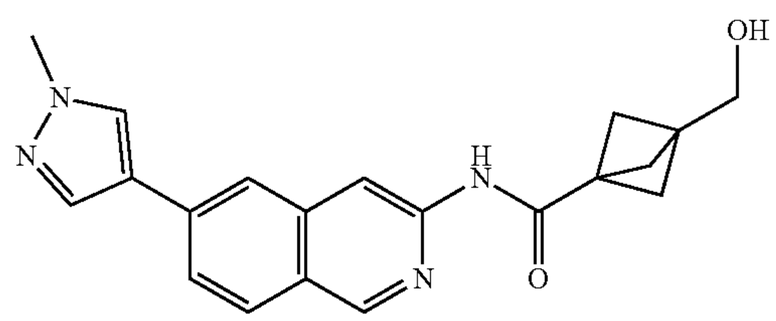
1082



trans-4-(Dimethylamino)-N-(6-(2-methyloxazol-5-yl)isoquinolin-3-yl) cyclohexane-1-carboxamide 1082

Brown solid (3.0 mg, 0.008 mmol, 4.6% yield). ^{1}H NMR (499 MHz, METHANOL-d_4) δ ppm 1.35-1.46 (2H, m), 1.60-1.72 (2H, m), 2.04-2.12 (4H, m), 2.37 (6H, s), 2.39-2.44 (1H, m), 2.44-2.53 (1H, m), 2.58 (3H, s), 7.61 (1H, s), 7.80 (1H, dd, J=8.51, 1.65 Hz), 8.03 (1H, d, J=8.51 Hz), 8.10 (1H, s), 8.48 (1H, s), 9.01 (1H, s); ESIMS found for $C_{22}H_{26}N_4O_2$ m/z 379.2 (M+1).

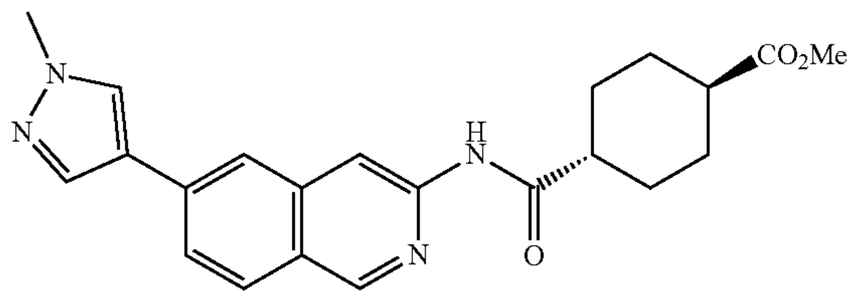
1083



3-(Hydroxymethyl)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl) bicyclo[1.1.1]pentane-1-carboxamide 1083

White solid (310.4 mg, 0.891 mmol, 96.0% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.97 (6H, s), 3.41 (2H, d, J=5.76 Hz), 3.90 (3H, s), 4.56 (1H, t, J=5.49 Hz), 7.76 (1H, dd, J=8.51, 1.65 Hz), 8.02 (1H, d, J=8.51 Hz), 8.04 (1H, s), 8.09 (1H, d, J=0.82 Hz), 8.37 (1H, s), 8.40 (1H, s), 9.05 (1H, s), 10.13 (1H, s); ESIMS found for $C_{20}H_{20}N_4O_2$ m/z 349.2 (M+1).

1084

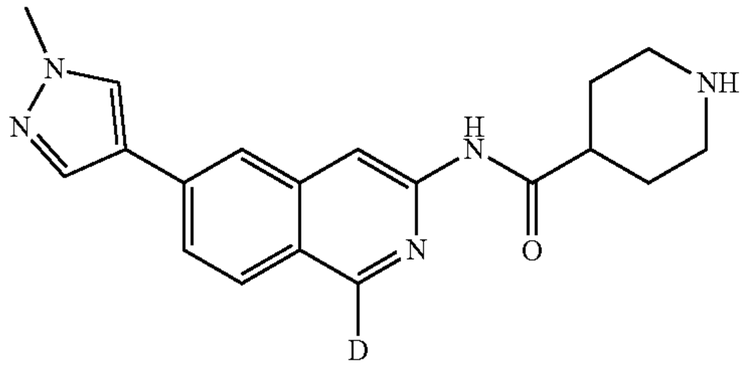


Methyl trans-4-((6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)carbamoyl) cyclohexane-1-carboxylate 1084

Light yellow solid (350.0 mg, 0.892 mmol, 40.0% yield). ^{1}H NMR (499 MHz, METHANOL-d_4) δ ppm 1.47-1.58 (2H, m), 1.64 (2H, qd, J=12.76, 2.88 Hz), 2.04 (2H, br dd,

J=13.31, 2.88 Hz), 2.09 (2H, br dd, J=13.31, 3.16 Hz), 2.39 (1H, tt, J=12.08, 3.57 Hz), 2.51 (1H, tt, J=11.87, 3.36 Hz), 3.68 (3H, s), 3.96 (3H, s), 7.73 (1H, dd, J=8.51, 1.65 Hz), 7.93-7.99 (2H, m), 8.00 (1H, s), 8.16 (1H, s), 8.40 (1H, s), 8.94 (1H, s); ESIMS found for $C_{22}H_{24}N_4O_3$ m/z 393.2 (M+1).

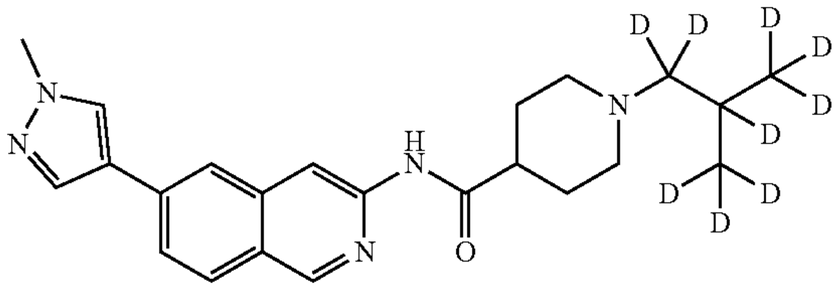
1085



N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl-1-d)piperidine-4-carboxamide 1085

Off-white solid (105.0 mg, 0.312 mmol, 81.1% yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.53 (2H, qd, J=12.12, 3.98 Hz), 1.70 (2H, br dd, J=12.21, 1.78 Hz), 2.44-2.49 (2H, m), 2.64 (1H, tt, J=11.60, 3.64 Hz), 2.94-3.01 (2H, m), 3.90 (3H, s), 7.74 (1H, dd, J=8.51, 1.65 Hz), 8.00 (1H, d, J=8.51 Hz), 8.03 (1H, d, J=1.37 Hz), 8.08 (1H, d, J=0.82 Hz), 8.35 (1H, s), 8.44 (1H, s), 10.40 (1H, s); ESIMS found for $C_{19}H_{20}[^2H]N_5O$ m/z 337.2 (M+1).

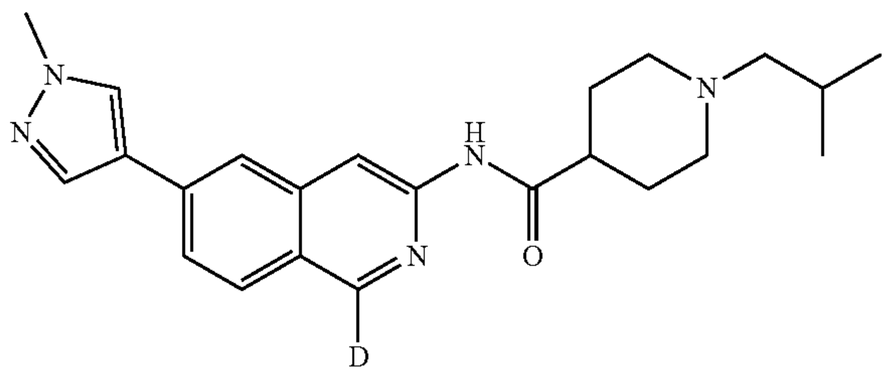
1086



N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-1-(2-(methyl-d_3)propyl-1,1,2,3,3,3-d_6)piperidine-4-carboxamide 1086

Beige solid (160.0 mg, 0.399 mmol, 67.0% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.61-1.73 (2H, m), 1.74-1.80 (2H, m), 1.86 (2H, td, J=11.66, 2.20 Hz), 2.51-2.58 (1H, m), 2.86 (2H, br d, J=11.25 Hz), 3.90 (3H, s), 7.74 (1H, dd, J=8.51, 1.65 Hz), 7.99 (1H, d, J=8.51 Hz), 8.04 (1H, s), 8.08 (1H, s), 8.35 (1H, s), 8.44 (1H, s), 9.02 (1H, s), 10.45 (1H, s); ESIMS found for $C_{23}H_{20}[^2H_9]N_5O$ m/z 401.3 (M+1).

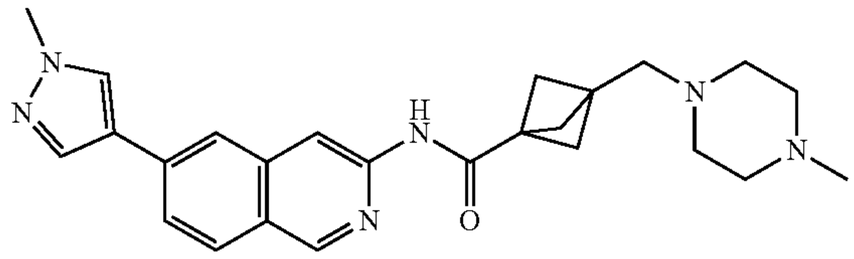
1087



1-Isobutyl-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl-1-d)piperidine-4-carboxamide 1087

White solid (75.0 mg, 0.191 mmol, 64.3% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 0.86 (6H, d, J=6.59 Hz), 1.63-1.73 (2H, m), 1.74-1.80 (3H, m), 1.83-1.90 (2H, m), 2.02 (2H, d, J=7.41 Hz), 2.51-2.57 (1H, m), 2.86 (2H, br d, J=11.25 Hz), 3.90 (3H, s), 7.74 (1H, dd, J=8.51, 1.65 Hz), 8.00 (1H, d, J=8.51 Hz), 8.04 (1H, d, J=1.37 Hz), 8.08 (1H, s), 8.35 (1H, s), 8.44 (1H, s), 10.45 (1H, s); ESIMS found for $C_{23}H_{28}[^2H]N_5O$ m/z 393.25 (M+1).

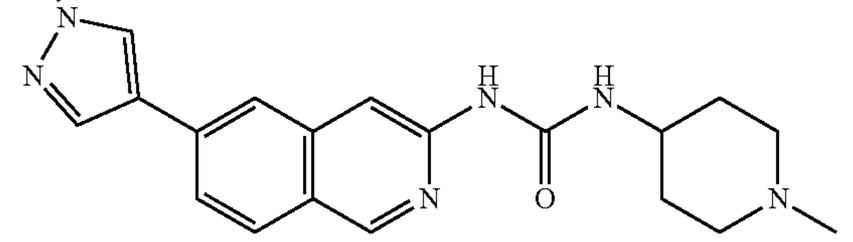
1088



N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-3-((4-methylpiperazin-1-yl)methyl)bicyclo[1.1.1]pentane-1-carboxamide 1088

Light brown amorphous solid (13.9 mg, 0.032 mmol, 30.2% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 2.04 (6H, s), 2.14 (3H, s), 2.31 (4H, br d, J=1.92 Hz), 2.36-2.46 (4H, m), 2.38 (2H, s), 3.90 (3H, s), 7.76 (1H, dd, J=8.51, 1.65 Hz), 8.01 (1H, d, J=8.51 Hz), 8.04 (1H, s), 8.09 (1H, s), 8.36 (1H, s), 8.39 (1H, s), 9.04 (1H, s), 10.13 (1H, s); ESIMS found for $C_{25}H_{30}N_6O$ m/z 431.25 (M+1).

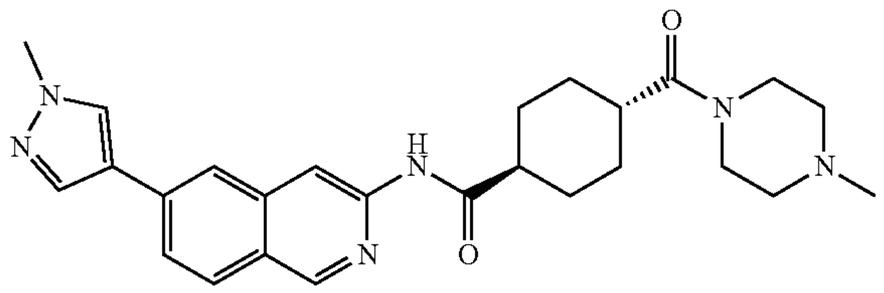
1090



1-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-3-(1-methylpiperidin-4-yl)urea 1090

Beige solid (35.0 mg, 0.096 mmol, 87.3% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.35-1.49 (2H, m), 1.77-1.88 (2H, m), 1.98-2.09 (2H, m), 2.17 (3H, s), 2.63 (2H, ddd, J=5.35, 3.43, 1.65 Hz), 3.54 (1H, br dd, J=4.12, 1.65 Hz), 3.90 (3H, s), 7.15-7.24 (1H, m), 7.65 (1H, dd, J=8.51, 1.65 Hz), 7.93 (3H, d, J=8.51 Hz), 8.07 (1H, s), 8.34 (1H, s), 8.88-8.96 (2H, m); ESIMS found for $C_{20}H_{24}N_6O$ m/z 365.2 (M+1).

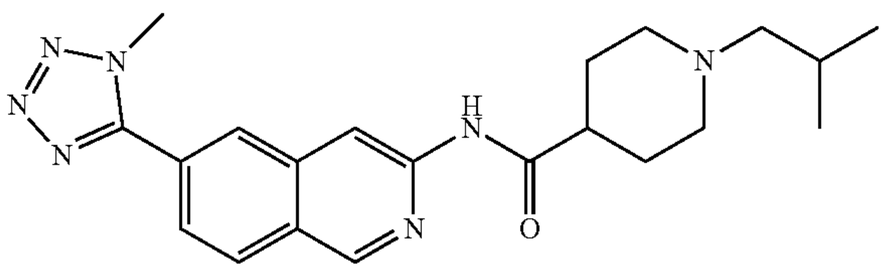
1091



trans-N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-4-(4-methylpiperazine-1-carbonyl)cyclohexane-1-carboxamide 1091

Beige solid (80.0 mg, 0.174 mmol, 50.6% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.35-1.47 (2H, m), 1.57 (2H, qd, J=12.76, 2.88 Hz), 1.69-1.75 (2H, m), 1.84-1.93 (2H, m), 2.18 (3H, s), 2.23 (2H, br s), 2.30 (2H, br s), 2.51-2.60 (1H, m), 2.64 (1H, tt, J=11.73, 3.22 Hz), 3.44 (2H, br s), 3.50 (2H, br s), 3.90 (3H, s), 7.74 (1H, dd, J=8.51, 1.65 Hz), 7.99 (1H, d, J=8.51 Hz), 8.04 (1H, s), 8.08 (1H, s), 8.35 (1H, s), 8.43 (1H, s), 9.02 (1H, s), 10.43 (1H, s); ESIMS found for $C_{26}H_{32}N_6O_2$ m/z 461.3 (M+1).

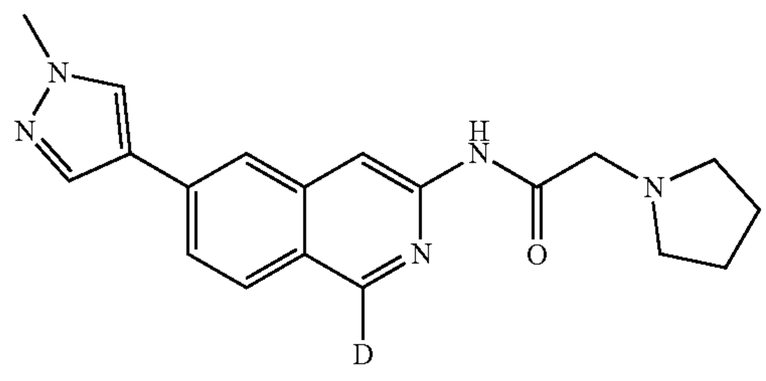
1092



1-Isobutyl-N-(6-(1-methyl-1H-tetrazol-5-yl)isoquinolin-3-yl)piperidine-4-carboxamide 1092. N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl-1-d)-2-(pyrrolidin-1-yl)acetamide

Off-white solid (18.0 mg, 0.046 mmol, 7.1% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 0.86 (6H, d, J=6.59 Hz), 1.61-1.72 (2H, m), 1.74-1.82 (3H, m), 1.82-1.94 (2H, m), 2.02 (2H, d, J=7.41 Hz), 2.52-2.61 (1H, m), 2.87 (2H, br d, J=11.53 Hz), 4.29 (3H, s), 7.92 (1H, dd, J=8.51, 1.65 Hz), 8.26 (1H, d, J=8.51 Hz), 8.44 (1H, s), 8.67 (1H, s), 9.27 (1H, s), 10.67 (1H, s); ESIMS found for $C_{21}H_{27}N_7O$ m/z 394.2 (M+1).

1093



N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl-1-d)-2-(pyrrolidin-1-yl) acetamide 1093

Beige solid (45.0 mg, 0.134 mmol, 44.6% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 1.78 (4H, dt, J=6.59, 3.29 Hz), 2.63-2.69 (4H, m), 3.35 (2H, s), 3.90 (3H, s), 7.77 (1H, dd, J=8.64, 1.51 Hz), 8.02 (1H, d, J=8.51 Hz), 8.10 (2H, s), 8.37 (1H, s), 8.43 (1H, s), 9.92 (1H, s); ESIMS found for $C_{19}H_{20}[^2H]N_5O$ m/z 337.2 (M+1).

Example 13

The screening assay for Wnt activity is described as follows. Reporter cell lines can be generated by stably transducing cancer cell lines (e.g., colon cancer) or primary cells (e.g., IEC-6 intestinal cells) with a lentiviral construct that includes a Wnt-responsive promoter driving expression of the firefly luciferase gene.

SW480 colon carcinoma cells were transduced with a lentiviral vector expressing luciferase with a human Sp5 promoter consisting of a sequence of eight TCF/LEF binding sites. SW480 cells stably expressing the Sp5-Luc reporter gene and a hygromycin resistance gene were selected by treatment with 150 μg/mL of hygromycin for 7 days. These stably transduced SW480 cells were expanded in cell culture and used for all further screening activities. Each compound was dissolved in DMSO as a 10 mM stock and used to prepare compound source plates. Serial dilution (1:3, 10-point dose-response curves starting from 10 μM) and compound transfer was performed using the ECHO 550 (Labcyte, Sunnyvale, Calif.) into 384-well white solid bottom assay plates (Greiner Bio-One) with appropriate DMSO backfill for a final DMSO concentration of 0.1%. For Sp5-Luc reporter gene assays, the cells were plated at 4,000 cells/well in 384-well plates with a DMEM medium containing 1% fetal bovine serum, and 1% Penicillin-Streptomycin and incubated for 36 to 48 hours at 37° C. and 5% CO_2. Following incubation, 15 μl of BriteLite Plus luminescence reagent (Perkin Elmer) was added to each well of the 384-well assay plates. The plates were placed on an orbital shaker for 2 min and then luminescence was quantified using the Envision (Perkin Elmer) plate reader. Readings were normalized to DMSO only treated cells, and normalized activities were utilized for EC_{50} calculations using the dose-response log (inhibitor) vs. response variable slope (four parameters) nonlinear regression feature available in GraphPad Prism 5.0 (or Dotmatics). For EC_{50} of >10 μM, the percent inhibition at 10 μM is provided.

Table 2 shows the measured activity for representative compounds of Formula I as described herein.

TABLE 2

Compound	EC_{50} (μM)
1	0.650
3	1.700
4	0.983
6	1.111
10	0.277
14	0.354
16	>10
69	3.700
71	3.900
72	0.920
73	0.485
75	0.520
76	0.705
77	0.610
78	1.000
81	0.735
82	4.950
83	2.900
84	1.900
85	1.200

TABLE 2-continued

Compound	EC_{50} (μM)
86	4.000
87	1.000
89	0.765
90	1.100
91	>10
92	1.600
96	>10
110	1.100
111	0.743
112	3.200
113	>10
114	0.835
115	2.400
116	7.100
118	3.600
119	1.060
120	2.205
121	3.500
188	>10
248	>10
262	1.700
263	1.300
264	>10
265	1.243
266	2.441
267	1.379
268	2.072
269	3.624
270	>10
271	1.715
272	3.753
273	1.511
274	3.720
275	1.917
276	5.183
277	5.264
278	0.413
279	5.650
280	2.325
281	>10 (47.0%)
282	>10 (49.3%)
283	2.486
284	1.874
285	3.405
286	3.143
287	7.330
288	1.197
289	2.647
290	5.231
291	4.641
292	3.385
293	3.222
294	5.186
295	2.571
296	3.479
297	4.811
298	3.229
299	1.529
300	1.117
301	0.467
302	3.646
303	9.831
304	2.317
305	1.942
306	3.698
307	>10 (25.9%)
308	1.809
309	>10 (43.5%)
310	1.462
311	0.578
312	>10 (23.8%)
313	0.577
314	0.859
315	1.588
316	2.845
317	1.266
318	0.442
320	1.142

TABLE 2-continued

Compound	EC_{50} (μM)
324	0.145
325	0.552
326	0.438
327	0.258
328	0.804
329	1.173
330	0.449
331	2.988
332	0.662
333	0.384
334	0.787
335	0.993
336	0.395
338	7.369
340	0.932
341	4.097
342	7.215
343	3.587
344	5.468
345	2.123
346	4.358
347	9.442
348	>10 (36.9%)
349	0.712
350	1.005
351	2.521
352	2.958
353	5.711
354	2.320
355	3.512
358	0.413
359	0.669
360	0.690
362	0.951
363	2.359
364	>10 (24.1%)
365	0.381
366	0.334
367	0.524
368	0.689
369	0.743
370	0.608
371	0.643
372	3.398
376	2.206
433	0.191
441	1.214
443	0.397
448	0.289
452	0.787
468	0.363
470	1.184
472	0.382
475	0.701
477	0.327
481	1.536
483	1.872
487	0.446
500	3.232
513	6.428
517	>10 (35.8%)
521	1.805
523	0.683
527	>10 (23.5%)
528	1.154
531	1.062
535	>10 (44.9%)
537	4.800
547	2.226
554	0.272
561	1.456
579	0.899
643	0.129
699	0.541
700	0.771
704	>10 (10.2%)
707	0.472
711	0.703

TABLE 2-continued

Compound	EC_{50} (μM)
713	9.246
718	0.589
731	3.046
737	1.291
741	0.444
743	9.487
758	1.253
760	3.970
767	3.225
773	6.549
784	5.885
785	2.837
791	0.212
795	0.471
798	0.594
803	3.551
822	0.517
826	0.603
831	0.706
839	0.776
851	>10 (6.4%)
883	>10 (43.2%)
885	4.475
888	1.038
900	1.013
921	0.779
932	0.946
939	2.072
946	1.881
952	1.469
953	>10 (48.7%)
959	4.235
960	1.658
962	>10 (45.0%)
963	1.199
964	1.449
965	3.175
966	1.592
967	4.423
968	>10 (38.0%)
969	3.926
970	1.356
971	0.720
972	0.420
973	0.609
974	3.742
975	0.423
976	2.965
977	0.875
978	2.223
979	4.093
980	>10 (40.5%)
981	1.085
982	2.709
983	5.533
984	2.987
985	1.160
986	1.380
987	>10 (10.7%)
988	>10 (11.1%)
989	4.320
990	2.865
991	1.705
992	3.209
993	7.974
994	7.901
995	>10 (43.8%)
996	4.389
997	3.886
998	2.249
999	3.100
1000	4.324
1001	0.593
1002	1.916
1003	1.315
1004	0.618
1005	1.396
1006	0.704

TABLE 2-continued

Compound	EC_{50} (μM)
1007	1.130
1008	3.350
1009	1.108
1010	2.021
1011	>10 (25.0%)
1012	2.718
1013	>10 (42.9%)
1014	2.364
1015	3.734
1016	4.057
1017	0.621
1018	0.608
1019	3.799
1020	1.142
1021	>10 (16.5%)
1022	1.370
1023	>10 (38.2%)
1024	3.510
1025	>10
1026	0.513
1027	0.875
1028	3.870
1029	3.336
1030	>10 (44.8%)
1031	3.969
1032	>10 (27.4%)
1034	2.040
1035	1.374
1037	3.643
1040	1.211
1041	0.776
1047	>10 (32.6%)
1048	9.381
1049	2.544
1051	0.480
1052	2.285
1057	>10 (5.0%)
1061	1.614
1064	4.119
1067	>10 (48.7%)
1068	3.718
1070	0.738
1071	>10 (43.2%)
1073	>10 (5.9%)
1074	>10 (19.7%)
1075	2.542
1076	0.640
1077	5.189
1078	4.033
1079	1.429
1080	1.218
1081	2.734
1082	9.902
1083	8.209
1084	3.407
1085	2.195
1086	0.485
1087	0.514
1088	7.403
1090	0.722
1091	2.949
1092	0.247
1093	1.781

Example 14

Representative compounds were screened using the assay procedure for DYRK1A kinase activity as described below.

Each compound was dissolved in DMSO as a 10 mM stock and used to prepare compound source plates. Serial dilution (1:3, 11-point dose-response curves from 10 μM to 0.00016 μM) and compound transfer was performed using the ECHO 550 (Labcyte, Sunnyvale, Calif.) into 1536-well black-walled round bottom plates (Corning).

The DYRK1A kinase assay was run using the Ser/Thr 18 peptide Z-lyte assay kit according to manufacturer's instructions (Life Technologies—a Division of Thermo-Fisher). This is a non-radioactive assay using fluorescence resonance energy transfer (FRET) between coumarin and fluorescein to detect kinase activity which is represented as a ratio of coumarin emission/fluorescein emission.

Briefly, recombinant DYRK1A kinase, ATP and Ser/Thr peptide 18 were prepared in 1× Kinase buffer to final concentrations of 0.19 μg/mL, 30 μM, and 4 μM respectively. The mixture was allowed to incubate with the representative compounds for one hour at room temperature. All reactions were performed in duplicate. Unphosphorylated ("0% Control") and phosphorylated ("100% control") forms of Ser/Thr 18 served as control reactions. Additionally, an 11-point dose-response curve of Staurosporine (1 uM top) was run to serve as a positive compound control.

After incubation, Development Reagent A was diluted in Development Buffer then added to the reaction and allowed to further incubate for one hour at room temperature. The plate was read at Ex 400 Em 455 to detect the coumarin signal and Ex 400 Em 520 to measure the signal (EnVision Multilabel Plate Reader, PerkinElmer).

The Emission ratio (Em) was calculated as a ratio of the coumarin (C) emission signal (at 445 nm)/Fluorescein (F) emission signal (at 520 nm). The percent phosphorylation was then calculated using the following formula: [1−((Em ratio×F100%)−C100%)/((C0%−C100%)+(Em ratio×(F100%−F0%)))]. Dose-response curves were generated and inhibitory concentration (IC_{50}) values were calculated using non-linear regression curve fit in the Dotmatics' Studies Software (Bishops Stortford, UK).

Table 3 shows the measured activity for representative compounds of Formula I as described herein.

TABLE 3

Compound	EC_{50} (μM)
1	0.0040
3	0.0037
4	0.0018
6	0.0013
10	0.0013
14	0.0015
16	0.0039
69	0.0062
71	0.0136
72	0.0025
73	0.0017
75	0.0026
76	0.0023
77	0.0016
78	0.0047
81	0.0015
82	0.0009
83	0.0012
84	0.0013
85	0.0014
86	0.0025
87	0.0033
89	0.0027
90	0.0030
91	0.0105
92	0.0065
96	0.0071
110	0.0047
111	0.0039
112	0.0206
113	0.0241
114	0.0019
115	0.0034
116	0.0043

TABLE 3-continued

Compound	EC_{50} (μM)
118	0.0096
119	0.0029
120	0.0048
121	0.0034
188	0.0286
248	0.0374
262	0.0015
263	0.0013
264	0.3476
265	0.0037
266	0.0174
267	0.0294
268	0.0058
269	0.0050
270	0.9524
271	0.0021
272	0.0140
273	0.0107
274	0.0059
275	0.0047
276	0.0051
277	0.0023
278	0.0032
279	0.0078
280	0.0108
281	0.0081
282	0.0115
283	0.0070
284	0.0071
285	0.0442
286	0.0649
287	5.1353
288	0.0273
289	0.0137
290	0.0058
291	0.0082
292	0.0078
293	0.0050
294	0.0124
295	0.0028
296	0.0143
297	0.0237
298	0.0135
299	0.0067
300	0.0082
301	0.0020
302	0.0077
303	0.0080
304	0.0027
305	0.0082
306	0.0072
307	6.2229
308	0.0024
309	0.0343
310	0.0062
311	0.0019
312	0.0127
313	0.0025
314	0.0221
315	0.0123
316	0.0042
317	0.0370
318	0.0588
320	0.0099
324	0.0021
325	0.0021
326	0.0029
327	0.0017
328	0.0019
329	0.0027
330	0.0016
331	0.0018
332	0.0035
333	0.0012
334	0.0016
335	0.0038
336	0.0029
338	0.0062

TABLE 3-continued

Compound	EC_{50} (μM)
340	0.0019
341	0.0056
342	0.0065
343	0.0099
344	0.0105
345	0.0040
346	0.0099
347	0.0104
348	0.0775
349	0.0065
350	0.0062
351	0.0136
352	0.0215
353	0.0086
354	0.0044
355	0.0064
358	0.0006
359	0.0030
360	0.0019
362	0.1319
363	0.0503
364	0.8403
365	0.0027
366	0.0106
367	0.0111
368	0.0079
369	0.0028
370	0.0031
371	0.0024
372	0.0106
376	0.0055
433	0.0019
441	0.0091
443	0.0022
448	0.0012
452	0.0004
468	0.0049
470	0.0027
472	0.0032
475	0.0032
477	0.0011
481	0.0043
483	0.0113
487	0.0077
500	0.0106
513	0.0104
517	0.0096
521	0.0016
523	0.0029
527	0.0098
528	0.0008
531	0.0009
535	0.0045
537	0.0089
547	0.0034
554	0.0014
561	0.0015
579	0.0250
643	0.0018
699	0.0021
700	0.0022
704	0.0082
707	0.0009
711	0.0010
713	0.0031
718	0.0013
731	0.0014
737	0.0010
741	0.0009
743	0.0013
758	0.0243
760	0.0038
767	0.0043
773	0.0038
784	0.0108
785	0.0101
791	0.0022
795	0.0024

TABLE 3-continued

Compound	EC_{50} (μM)
798	0.0031
803	0.0126
822	0.0041
826	0.0039
831	0.0032
839	0.0038
851	5.0052
883	0.0089
885	0.0346
888	0.0014
900	0.0029
921	0.0021
932	0.0169
939	0.0139
946	0.0230
952	0.0072
953	0.0168
959	0.0154
960	0.0171
962	0.0236
963	0.0267
964	0.0052
965	0.0106
966	0.0020
967	0.0019
968	0.0314
969	0.0500
970	0.0023
971	0.0342
972	0.0030
973	0.0029
974	0.0135
975	0.0120
976	0.0061
977	0.0032
978	0.0039
979	0.0100
980	0.0191
981	0.0137
982	0.0192
983	0.0223
984	0.0055
985	0.0041
986	0.0110
987	0.0428
988	0.0249
989	0.0162
990	0.0213
991	0.0033
992	0.0253
993	0.0147
994	0.0129
995	0.0133
996	0.0134
997	0.1864
998	0.0062
999	0.0209
1000	0.0111
1001	0.0073
1002	0.0285
1003	0.0021
1004	0.0020
1005	0.0015
1006	0.0030
1007	0.0024
1008	0.0075
1009	0.0062
1010	0.0026
1011	0.0026
1012	0.0130
1013	0.0171
1014	0.0094
1015	0.0058
1016	0.0291
1017	0.0031
1018	0.0025
1019	0.0289
1020	0.0104

TABLE 3-continued

Compound	EC_{50} (μM)
1021	0.0422
1022	0.0042
1023	0.0087
1024	0.0170
1025	0.0780
1026	0.0050
1027	0.0500
1028	0.0225
1029	0.0257
1030	0.1938
1031	0.0704
1032	0.0012
1034	0.0019
1035	0.0026
1037	0.0102
1040	0.0048
1041	0.0033
1047	0.4629
1048	0.5407
1049	0.0069
1051	0.0146
1052	0.0180
1057	0.0027
1061	0.0043
1064	0.0067
1067	0.0188
1068	0.0053
1070	0.0076
1071	0.0165
1073	1.5241
1074	0.0069
1075	0.0137
1076	0.0084
1077	0.0045
1078	0.0060
1079	0.0057
1080	0.0032
1081	0.0022
1082	0.0102
1083	0.0042
1084	0.0017
1085	0.0024
1086	0.0025
1087	0.0035
1088	0.0093
1090	0.0069
1091	0.0014
1092	0.0627
1093	0.0117

Example 15

Representative compounds were screened using the assay procedure for GSK3β kinase activity as described below.

Each compound is dissolved in DMSO as a 10 mM stock and used to prepare compound source plates. Serial dilution (1:3, 11-point dose-response curves from 10 μM to 0.0003 μM) and compound transfer was performed using the ECHO 550 (Labcyte, Sunnyvale, Calif.) into 1536-well black-walled round bottom plates (Corning).

The GSK3β kinase assay is run using the Ser/Thr 09 peptide Z-lyte assay kit according to manufacturer's instructions (Life Technologies—a Division of Thermo-Fisher). This is a non-radioactive assay using fluorescence resonance energy transfer (FRET) between coumarin and fluorescein to detect kinase activity which is represented as ratio of coumarin emission/fluorescein emission.

Briefly, recombinant GSK3β kinase, ATP and Ser/Thr peptide 09 are prepared in 1× Kinase buffer to final concentrations of 0.04 μg/mL, 46 μM, and 4 μM respectively. The mixture is allowed to incubate with the representative compounds for one hour at room temperature. All reactions were performed in duplicate. Unphosphorylated ("0% Control") and phosphorylated ("100% control") forms of Ser/Thr 18 serve as control reactions.

After incubation, diluted Development Buffer is added to the reaction and allowed to further incubate for one hour at room temperature. The plate is read at Ex 400 Em 455 to detect the coumarin signal and Ex 400 Em 520 to measure the signal (EnVision Multilabel Plate Reader, PerkinElmer).

The Emission ratio (Em) is calculated as a ratio of the coumarin (C) emission signal (at 445 nm)/Fluorescein (F) emission signal (at 520 nm). The percent phosphorylation is then calculated using the following formula: [1−((Em ratio× F100%)−C100%)/((C0%−C100%)+(Em ratio×(F100%−F0%)))].

Dose-response curves are generated and inhibitory concentration (IC_{50}) values are calculated using non-linear regression curve fit in the Dotmatics' Studies Software (Bishops Stortford, UK).

Table 4 shows the activity of representative compounds of Formula I as provided herein.

TABLE 4

Compound	EC_{50} (μM)
1	0.008
3	0.038
4	0.080
6	0.065
10	0.051
14	0.059
16	0.024
69	0.013
71	0.062
72	0.064
73	0.049
75	0.064
76	0.031
77	0.024
78	0.063
81	0.030
82	0.022
83	0.034
84	0.020
85	0.029
86	0.048
87	0.032
89	0.064
90	0.042
91	0.838
92	0.361
96	0.350
110	0.034
111	0.040
112	0.292
113	0.586
114	0.032
115	0.030
116	0.024
118	0.079
119	0.007
120	0.138
121	0.053
188	0.265
248	0.266
262	0.024
263	0.018
264	>10
265	0.007
266	0.038
267	0.039
268	0.017
269	1.022
270	5.310
271	0.003
272	0.105
273	0.048

TABLE 4-continued

Compound	EC_{50} (μM)
274	0.025
275	0.115
276	0.006
277	0.104
278	0.007
279	0.014
280	0.185
281	0.071
282	0.134
283	0.062
284	0.037
285	0.149
286	0.186
287	9.838
288	0.020
289	0.062
290	0.075
291	0.043
292	0.173
293	0.059
294	0.041
295	0.020
296	0.080
297	0.155
298	0.125
299	0.044
300	0.031
301	0.010
302	0.038
303	0.089
304	0.029
305	0.051
306	0.066
307	5.256
308	0.107
309	0.120
310	0.105
311	0.020
312	0.031
313	0.039
314	0.012
315	0.044
316	0.509
317	0.030
318	0.012
320	0.010
324	0.030
325	0.003
326	0.019
327	0.066
328	0.016
329	0.029
330	0.015
331	0.055
332	0.039
333	0.060
334	0.047
335	0.071
336	0.083
338	0.067
340	0.257
341	0.089
342	0.137
343	0.071
344	0.175
345	0.026
346	0.084
347	0.165
348	0.221
349	0.066
350	0.033
351	0.130
352	0.110
353	0.029
354	0.037
355	0.228
358	0.080
359	0.082

TABLE 4-continued

Compound	EC_{50} (μM)
360	0.047
362	1.102
363	0.035
364	3.122
365	0.052
366	0.116
367	0.056
368	0.051
369	0.101
370	0.089
371	0.023
372	0.079
376	0.710
433	0.001
441	0.005
443	0.013
448	0.011
452	0.007
468	0.007
470	0.004
472	0.008
475	0.023
477	0.006
481	0.004
483	0.045
487	0.007
500	0.023
513	0.043
517	0.470
521	0.234
523	0.042
527	0.415
528	0.096
531	0.050
535	0.087
537	0.095
547	0.104
554	0.038
561	0.012
579	0.048
643	0.049
699	0.024
700	0.049
704	1.831
707	0.046
711	0.067
713	0.098
718	0.079
731	0.042
737	0.062
741	0.107
743	0.063
758	0.050
760	0.133
767	0.157
773	0.219
784	0.133
785	0.044
791	0.005
795	0.033
798	0.031
803	0.164
822	0.009
826	0.007
831	0.010
839	0.017
851	5.005
883	0.076
885	0.046
888	0.008
900	0.011
921	0.005
932	0.014
939	0.013
946	0.038
952	0.008
953	0.023
959	0.045

TABLE 4-continued

Compound	EC_{50} (μM)
960	0.015
962	0.057
963	0.006
964	0.102
965	0.079
966	0.032
967	0.046
968	0.061
969	7.613
970	0.478
971	0.034
972	0.064
973	0.020
974	0.096
975	1.094
976	0.146
977	0.246
978	0.220
979	0.791
980	0.389
981	0.141
982	0.265
983	0.303
984	0.236
985	0.283
986	0.021
987	2.316
988	1.093
989	0.298
990	0.100
991	0.029
992	0.014
993	0.087
994	0.110
995	0.177
996	0.141
997	0.033
998	0.102
999	0.086
1000	0.270
1001	0.009
1002	0.425
1003	0.043
1004	0.037
1005	0.032
1006	0.050
1007	0.083
1008	0.091
1009	0.015
1010	0.053
1011	0.030
1012	0.155
1013	1.429
1014	0.096
1015	0.101
1016	0.087
1017	0.076
1018	0.054
1019	0.158
1020	0.013
1021	1.585
1022	0.124
1023	0.838
1024	0.150
1025	0.100
1026	0.508
1027	3.073
1028	0.104
1029	0.018
1030	0.390
1031	0.380
1032	0.072
1034	0.027
1035	0.010
1037	1.923
1040	0.098
1041	0.058
1047	4.745

TABLE 4-continued

Compound	EC_{50} (μM)
1048	5.812
1049	0.012
1051	0.009
1052	0.011
1057	0.097
1061	0.008
1064	0.126
1067	0.067
1068	0.036
1070	0.016
1071	2.733
1073	>10
1074	0.278
1075	0.015
1076	0.011
1077	0.032
1078	0.070
1079	0.048
1080	0.056
1081	0.082
1082	0.210
1083	0.914
1084	0.040
1085	0.083
1086	0.028
1087	0.037
1088	0.937
1090	0.288
1091	0.069
1092	0.132
1093	0.047

Example 16

Representative compounds were screened using the assay procedure for tau phosphorylation activity described below.

SH-SY5Y cells (human neuroblastoma) were cultured in DMEM/F-12 medium supplemented with 15% FBS, Non-essential Amino Acid and Penicillin/Streptomycin. Two days before treatment, cells were seeded onto 96 well plates at 5×10^4 cells/well.

The above synthesized compounds were screened using the cell assay procedure to assess decrease Tau phosphorylation at Ser396 (pSer396) described below.

DMSO-resuspended compounds were dispensed to 8 wells as a serial titration from 10 μM to 4.6 nM final in medium and cells were exposed overnight (16-18 h) in a humidified incubator at 36.6 c before harvest. Wells were visually checked for cell death or change in morphology and supernatants were tested for cytotoxicity by measurement of lactate dehydrogenase release (LDH, CytoToxOne kit, Promega) if necessary. As controls, commercially available DYRK1A inhibitors, Harmine and Indy which were shown to have good DYRK1A inhibition in the kinase assay with no CDK1 activity (EC_{50} 18 and 53 nM respectively, 6 μM for CDK1) but weak EC_{50} in the Tau assay >10 μM.

Cells were lysed with RIPA buffer complemented with phosphatase and protease inhibitors then lysates were spun down at 12,000 g for 10 min to remove any cellular debris. Lysates are then either directly tested for pSer396 by ELISA (Life Technology, Kit KHB7031) or loaded on NuPage Bis-Tris gels for western blot analysis. Colorimetric detection of ELISA signal is performed by Cytation3 plate reader (Biotek) and the chemiluminescence signal for HRP-linked antibodies used in western blotting is detected using a Carestream Image Station. The same pSer396 antibody is used for detection of pTau in both assays.

Blot densitometry for pSer396 and β-actin were analyzed using ImageJ (NIH) and pSer396 Tau ELISA signal was used to plot, draw the curve fitting, and determine each compounds EC_{50} in Prism (GraphPad).

Table 5 shows the activity of representative compounds as provided herein.

TABLE 5

Compound	pSer396 Tau EC_{50} (μM)
1	0.149
3	0.288
4	0.671
6	0.475
10	0.227
14	0.408
16	>10
69	0.383
71	1.510
72	0.757
73	0.199
75	0.227
76	0.219
77	0.184
78	0.265
81	0.452
82	0.315
83	0.432
84	0.454
85	0.392
86	0.682
87	0.414
89	0.364
90	0.302
91	4.700
92	3.900
96	2.000
110	0.636
111	0.597
112	1.750
113	3.800
114	0.286
115	0.311
116	0.870
118	1.200
119	0.418
121	1.030
188	4.220
248	0.905
262	0.174
263	0.119
264	>10
265	0.656
266	1.200
267	0.555
268	0.478
269	4.300
270	>10
271	0.124
272	1.660
273	0.492
274	0.535
275	0.232
276	0.150
277	1.080
278	0.076
279	0.498
280	0.677
281	0.518
282	0.973
283	0.411
284	0.359
285	1.580
286	1.150
288	0.159
289	0.185
290	0.490
291	0.716

TABLE 5-continued

Compound	pSer396 Tau EC_{50} (μM)
292	1.350
293	0.668
294	0.905
295	0.430
296	0.978
297	1.420
298	1.390
299	0.573
300	0.222
301	0.108
302	0.628
303	0.783
304	0.210
305	0.247
306	0.592
307	2.080
308	0.361
309	1.220
310	0.628
311	0.163
312	0.762
313	0.330
314	0.128
315	0.346
316	8.780
317	0.200
318	0.072
320	0.280
324	0.180
325	0.440
326	0.574
327	0.411
328	0.231
329	0.524
330	0.246
331	0.311
332	0.249
333	1.100
334	0.820
335	0.289
336	0.820
338	1.700
340	2.300
341	1.600
342	3.600
343	2.400
344	3.500
345	0.774
346	1.800
347	4.400
348	2.000
349	0.351
350	0.417
351	0.846
352	1.300
353	0.724
354	1.200
355	1.700
358	0.353
359	0.521
360	0.659
363	0.406
364	>10
365	1.200
366	1.100
367	0.258
368	0.660
369	0.970
370	0.256
371	0.581
372	1.100
376	7.900
433	0.032
441	0.073
443	0.289
448	0.106
452	0.912

TABLE 5-continued

Compound	pSer396 Tau EC_{50} (μM)
468	0.039
470	0.095
472	0.200
475	1.800
477	0.188
481	0.662
483	0.611
487	0.161
500	0.388
513	0.864
517	1.300
521	1.100
523	2.200
527	2.400
528	0.323
531	0.146
535	6.200
537	0.451
547	0.379
554	0.095
561	0.395
579	0.062
643	0.049
699	0.423
700	0.513
704	10.000
707	0.449
711	0.443
713	5.000
718	0.294
731	0.450
737	0.865
741	0.528
743	0.432
758	0.384
760	1.200
767	1.000
773	2.200
784	2.200
785	0.485
791	0.055
795	0.401
798	0.320
803	3.700
822	0.247
826	0.568
831	0.189
839	0.254
851	0.350
883	1.100
885	0.878
888	0.195
900	0.180
921	0.109
932	0.357
939	0.274
946	0.571
952	0.269
953	0.398
959	0.443
960	0.233
962	0.447
963	0.252
964	0.576
965	1.000
966	0.236
967	0.373
968	2.700
970	0.862
971	0.191
972	0.355
973	0.102
974	2.000
975	4.600
976	0.536
977	0.426
978	0.274

TABLE 5-continued

Compound	pSer396 Tau EC_{50} (μM)
979	0.569
980	2.100
981	1.100
982	1.100
983	1.500
984	2.100
985	3.200
986	0.387
987	>10
988	>10
989	>10
990	1.800
991	10.000
992	0.350
993	0.702
994	1.900
995	2.400
996	3.100
997	1.300
998	0.638
999	0.659
1000	1.500
1001	3.300
1002	1.900
1003	0.732
1004	0.667
1005	0.898
1006	0.296
1007	0.435
1008	0.643
1009	0.068
1010	0.622
1011	>10
1012	0.555
1013	4.200
1014	0.767
1015	0.523
1016	0.631
1017	0.320
1018	0.280
1019	1.500
1020	0.049
1021	5.700
1022	9.600
1023	1.800
1024	1.200
1025	>10
1027	2.200
1028	0.536
1029	0.239
1030	1.200
1031	0.969
1034	0.430
1035	0.129
1037	>10
1040	1.600
1041	1.300
1047	>10
1048	4.700
1049	0.319
1051	0.147
1052	0.254
1057	0.342
1061	0.058
1064	0.109
1067	0.729
1068	0.689
1070	0.091
1071	6.900
1074	1.300
1075	0.709
1076	0.041
1077	0.425
1078	0.458
1079	0.190
1080	0.251
1081	0.470

TABLE 5-continued

Compound	pSer396 Tau EC_{50} (μM)
1082	1.100
1086	0.168
1087	0.160
1088	8.600
1090	0.969
1091	0.869
1092	0.131
1093	0.422

Example 17

Representative compounds were screened using the cell-based assay procedure for secreted β-amyloid 40 (Aβ40) peptide in an APP overexpressing cell line described below.

SH-SY5Y cells (human neuroblastoma) were cultured in 1:1 DMEM/F-12 medium supplemented with 15% FBS, 1% non-essential amino acids, and 1% penicillin/streptomycin. HEK293T cells (human kidney) were cultured in DMEM medium supplemented with 10% FBS and 1% penicillin/streptomycin.

SH-SY5Y cells were infected with lentivirus to overexpress amyloid (A4) beta precursor protein (APP), hereafter referred to as the SH-SY5Y-APP cells. Specifically, in a 10 cm dish, HEK293T cells were seeded at

$$2.5\times10^{5}\ \frac{\text{cells}}{\text{mL}}$$

and transfected with APP (Myc-DDK-tagged)-Human amyloid beta (A4) precursor protein (APP), transcript variant 3 pLenti-ORF expression construct (custom modification of RC215147 to include bicistronic IRES-puromycin, OriGene). Culture medium was changed 18 h post-transfection before a first batch of viral supernatant was then harvested at 42 h post-transfection. Culture medium was replenished once more before a second batch of viral supernatant was harvested 66 h post-transfection. The two batches of viral supernatant were combined and spun at 1800 g, then filtered through a 0.45 μm PVDF filter.

SH-SY5Y cells were seeded onto 6-well plates at

$$5.0\times10^{5}\ \frac{\text{cells}}{\text{well}}$$

and incubated overnight at 37° C. Cells were then infected with viral supernatant at concentrations ranging from 10%→100% viral supernatant (diluted in Opti-MEM as appropriate), with

$$10\ \frac{\mu\text{g}}{\text{mL}}$$

Polybrene added for permeability (H9268, Sigma). 24 hours post-transfection, the entire volume from each well was replaced with regular SH-SY5Y medium. 4 days post-transfection, APP-overexpressing SH-SY5Y cells were selected for by adding puromycin (A11138-03, Gibco) to each well at a final concentration of

$$2\ \frac{\mu\text{g}}{\text{mL}}.$$

Puromycin-resistant cell were then expanded, harvested and banked. APP-overexpression was controlled by immunoblotting for total APP and Myc-DDK.

The cell assay procedure start 18 h prior to treatment, as SH-SY5Y-APP cells were seeded onto 96-well plates at

$$2.0\times10^{4}\ \frac{\text{cells}}{\text{well}}.$$

The entire 200 μL volume of medium was removed from all wells, and replenished to reset any Aβ40 peptide that may have been secreted prior to treatment. DMSO-resuspended compounds were dispensed to eight wells as a serial dilution from 10 μM to 4.6 nM final concentration in medium. At this time, designated wells were seeded with SH-SY5Y cells that were seeded and treated with puromycin at

$$10\ \frac{\mu\text{g}}{\text{mL}}.$$

Cells were exposed overnight (16-18 hours) in a 37° C. incubator before supernatant was harvested. Wells were visually checked for cell death before 150 μL of supernatant was harvested from each well into V-bottom 96-well plates (3894, Corning). The original plates with seeded cells were tested for cytotoxicity by measure of adenosine triphosphate (ATP) release by adding CellTiter-Glo® diluted 1:4 in distilled water (G7573, Promega) and transferring lysed cells to a completely black 96-well plate to be read with the Cytation3. Plates containing supernatant were spun down at 1200 g for 10 minutes to remove any cellular debris. Supernatant was then diluted 1:2 with a diluent from V-PLEX Aβ40 Peptide (6E10) Kit and directly tested for secreted Aβ40 peptide (K150SKE, Meso Scale Discovery). The signal was used to plot, draw the curve fitting, and determine each compounds EC_{50} in Prism (GraphPad).

Table 6 shows the activity of representative compounds as provided herein.

TABLE 6

Compound	Aβ40 IC_{50} (μM)
1	3.96
72	2.1
76	1.2
77	1.1
78	0.889
81	2.3
82	5.1
83	>10
84	4.4
85	1.3
111	0.272
115	0.956
248	>10
262	2.2
263	5.3
269	>10
271	4.6

Example 18

Representative compounds were screened using the assay procedure to assess the effect on cell viability as described below.

SW480 colon carcinoma cells were transduced with a lentiviral vector expressing luciferase with a human Sp5 promoter consisting of a sequence of eight TCF/LEF binding sites. SW480 cells stably expressing the Sp5-Luc reporter gene and a hygromycin resistance gene were selected by treatment with 150 μg/mL of hygromycin for 7 days. These stably transduced SW480 cells were expanded in cell culture and used for all further screening activities. Each compound was dissolved in DMSO as a 10 mM stock and used to prepare compound source plates. Serial dilution (1:3, 8-point dose-response curves from 10 μM to 0.0045 μM) and compound transfer was performed using the ECHO 550 (Labcyte, Sunnyvale, Calif.) into 384-well white solid bottom assay plates (Greiner Bio-One) with appropriate DMSO backfill for a final DMSO concentration of 0.1%.

For the Cell Viability Assays, the cells were plated at 2,000 cells/well in 384-well plates with a DMEM medium containing 1% fetal bovine serum, and 1% Penicillin-Streptomycin and incubated for four days hours at 37° C. and 5% CO_2. Eight replicates of DMSO-treated cells served as controls and cells treated with compound were performed in duplicate.

After incubation, 10 μL of CellTiter-Glo (Promega) was added to each well allowed to incubate for approximately 12 minutes. This reagent "results in cell lysis and generation of a luminescent signal proportional to the amount of ATP present. The amount of ATP is directly proportional to the number of cells present in culture, in agreement with previous reports. The CellTiter-Glo® Assay generates a "glow-type" luminescent signal, produced by the luciferase reaction (Promega.com)".

After incubation, the plates were read at Ex 560 nm Em 590 nm (Cytation 3, BioTek). Dose-response curves were generated and EC_{50} concentration values were calculated using non-linear regression curve fit in the GraphPad Prism (San Diego, Calif.) or Dotmatics' Studies Software (Bishops Stortford, UK). For EC_{50} of >10 μM, the percent inhibition at 10 μM is provided.

Table 7 shows the activity of representative compounds of Formula I as provided herein.

TABLE 7

Compound	EC_{50} (μM)
1	0.130
3	2.802
4	1.937
6	1.256
10	0.324
14	0.898
16	7.845
69	3.931
71	8.098
72	0.911
73	0.769
75	1.322
76	1.556
77	0.767
78	1.844
81	0.949
82	2.710
83	6.336
84	1.954
85	1.637
86	>10
87	3.156
89	0.738
90	1.174
91	9.592
92	0.983
96	>10
110	1.049
111	0.526
112	6.425
113	>10
114	3.892
115	3.505
116	6.495
118	5.936
119	0.525
120	2.486
121	4.307
188	>10
248	>10
262	1.391
263	1.287
264	8.750
265	4.348
266	6.316
267	2.025
268	2.774
269	2.3303
270	>10
271	2.962
272	5.869
273	1.184
274	4.051
275	1.275
276	>10 (29.6%)
277	1.401
278	1.232
279	>10 (52.4%)
280	9.566
281	>10
282	6.613
283	3.121
284	2.670
285	7.023
286	3.292
287	>10 (47.8%)
288	2.660
289	7.755
290	3.783
291	>10 (24.4%)
292	2.821
293	2.857
294	4.154
296	3.465
297	5.718
298	2.381
299	2.237
300	1.298
301	0.550
302	>10 (34.9%)
303	7.804
304	1.338
305	1.651
306	3.199
307	>10
308	>10 (32.0%)
309	>10 (9.6%)
310	5.347
311	0.751
312	>10
313	0.711
314	1.196
315	1.251
316	2.340
317	6.336
318	0.940
320	1.784
324	0.266

TABLE 7-continued

Compound	EC_{50} (μM)
325	0.526
326	0.400
327	1.585
328	0.929
329	4.119
330	6.784
331	3.115
332	1.003
333	0.641
334	7.370
335	1.120
336	0.510
338	9.332
340	2.232
341	>10 (33.9%)
342	>10 (40.0%)
343	7.886
344	7.678
345	3.076
346	9.663
347	>10 (48.5%)
348	>10 (22.4%)
349	0.704
350	1.081
351	6.882
352	8.599
353	8.225
354	4.992
355	8.634
358	2.372
359	0.261
360	0.570
362	5.476
363	3.057
364	5.601
365	0.522
366	0.910
367	8.240
368	0.651
369	0.864
370	1.246
371	1.063
372	8.816
376	4.195
433	0.615
441	5.268
443	1.676
448	0.626
452	1.453
468	2.507
470	4.187
472	5.093
475	1.063
477	0.719
481	1.368
483	7.343
487	2.684
500	>10 (25.1%)
513	9.064
517	>10 (27.5%)
521	3.629
523	0.447
527	>10 (43.6%)
528	1.415
531	0.989
535	>10 (42.0%)
537	8.303
547	0.931
554	0.366
561	0.924
579	0.954
643	0.115
699	0.834
700	0.623
704	>10 (18.1%)
707	0.947
711	0.706
713	6.976

TABLE 7-continued

Compound	EC_{50} (μM)
718	0.483
731	1.103
737	4.342
741	0.462
743	1.544
758	1.336
760	3.284
767	9.054
773	>10 (48.4%)
784	>10 (39.7%)
785	2.860
791	0.137
795	0.806
798	0.613
803	4.533
822	0.708
826	0.897
831	0.911
839	1.177
851	>10 (30.4%)
883	>10 (35.5%)
885	7.720
888	2.471
900	3.883
921	1.624
932	5.449
939	>10 (31.6%)
946	>10 (42.6%)
952	7.090
953	>10 (40.3%)
959	>10 (45.0%)
960	6.673
962	>10 (30.9%)
963	>10 (49.2%)
964	3.828
965	8.630
966	0.259
967	0.459
968	>10 (14.5%)
969	2.885
970	1.255
971	1.197
972	0.757
973	0.391
974	3.161
975	0.334
976	3.878
977	0.615
978	1.577
979	2.223
980	5.743
981	0.546
982	1.212
983	4.619
984	3.128
985	1.722
986	3.305
987	>10 (10.6%)
988	>10 (18.0%)
989	>10 (36.4%)
990	3.547
991	3.957
992	5.599
993	6.585
994	>10 (36.8%)
995	>10 (47.6%)
996	>10 (32.2%)
997	5.060
998	4.753
999	7.514
1000	7.295
1001	0.677
1002	>10 (37.6%)
1003	0.804
1004	0.678
1005	1.126
1006	0.584
1007	0.922

TABLE 7-continued

Compound	EC_{50} (μM)
1008	>10 (37.2%)
1009	2.351
1010	3.965
1011	>10 (25.0%)
1012	3.195
1013	5.498
1014	5.417
1015	6.419
1016	6.136
1017	0.659
1018	0.498
1019	9.381
1020	1.032
1021	>10 (11.6%)
1022	3.337
1023	>10 (39.9%)
1024	6.773
1026	0.554
1027	0.488
1028	3.523
1029	>10 (34.6%)
1030	>10 (19.3%)
1031	3.892
1032	>10 (34.7%)
1034	3.242
1035	2.463
1037	>10 (32.7%)
1040	2.684
1041	2.763
1047	>10 (41.7%)
1048	4.057
1049	>10 (31.3%)
1051	>10 (22.5%)
1052	>10 (40.7%)
1057	4.505
1061	1.595
1064	4.851
1067	>10 (43.1%)
1068	>10 (46.0%)
1070	8.388
1071	>10 (26.2%)
1073	>10 (8.5%)
1074	>10 (25.0%)
1075	5.281
1076	1.576
1077	5.246
1078	4.407
1079	2.605
1080	1.380
1081	4.648
1082	7.100
1083	0.901
1084	3.666
1085	1.240
1086	0.592
1087	0.746
1088	9.194
1090	0.994
1091	1.246
1092	2.984

Example 19

Representative compounds were screened using primary human fibroblasts (derived from IPF patients) treated with TGF-β1 to determine their ability to inhibit the fibrotic process.

Human Fibroblast Cell Culture:

Primary human fibroblasts derived from IPF patients (LL29 cells) [[1]Xiaoqiu Liu, et. al., "Fibrotic Lung Fibroblasts Show Blunted Inhibition by cAMP Due to Deficient cAMP Response Element-Binding Protein Phosphorylation", *Journal of Pharmacology and Experimental Therapeutics* (2005), 315(2), 678-687; [2]Watts, K. L., et. al., "RhoA signaling modulates cyclin D1 expression in human lung fibroblasts; implications for idiopathic pulmonary fibrosis", *Respiratory Research* (2006), 7(1), 88] were obtained from American Type Culture Collection (ATCC) and expanded in F12 medium supplemented with 15% Fetal Bovine Serum and 1% Penicillin/Streptomycin.

Compound Screening:

Each compound was dissolved in DMSO as a 10 mM stock and used to prepare compound source plates. Serial dilution (1:2, 11-point dose-response curves from 10 μM to 0.94 nM) and compound transfer was performed using the ECHO 550 (Labcyte, Sunnyvale, Calif.) into 384-well clear bottom assay plates (Greiner Bio-One) with appropriate DMSO backfill for a final DMSO concentration of 0.1%. LL29 cells were plated at 1,500 cells/well in 70 μL/well F12 medium supplemented with 1% Fetal Bovine Serum. TGF-β1 (Peprotech; 20 ng/mL) was added to the plates to induce fibrosis (ref. 1 and 2 above). Wells treated with TGF-β1 and containing DMSO were used as positive control, and cells with only DMSO were negative control. Cells were incubated at 37° C. and 5% CO_2 for 4 days. Following incubation for 4 days, SYTOX green nucleic acid stain (Life Technologies [Thermo Fisher Scientific]) was added to the wells at a final concentration of 1 μM and incubated at room temperature for 30 min. Cells were then fixed using 4% formaldehyde (Electron Microscopy Sciences), washed 3 times with PBS followed by blocking and permeabilization using 3% Bovine Serum Albumin (BSA; Sigma) and 0.3% Triton X-100 (Sigma) in PBS. Cells were then stained with antibody specific to α-smooth muscle actin (αSMA; Abcam) (ref 1 and 2 above) in 3% Bovine Serum Albumin (BSA; Sigma) and 0.3% Triton X-100 (Sigma) in PBS, and incubated overnight at 4° C. Cells were then washed 3 times with PBS, followed by incubation with Alexa Flor-647 conjugated secondary antibody (Life Technologies [Thermo Fisher Scientific]) and DAPI in 3% Bovine Serum Albumin (BSA; Sigma) and 0.3% Triton X-100 (Sigma) in PBS at room temperature for 1 hour. Cells were then washed 3 times with PBS and plates were sealed for imaging. αSMA staining was imaged by excitation at 630 nm and emission at 665 nm and quantified using the Compartmental Analysis program on the CellInsight CX5 (Thermo Scientific). Dead or apoptotic cells were excluded from analysis based on positive SYTOX green staining. % of total cells positive for αSMA were counted in each well and normalized to the average of 11 wells treated with TGF-β1 on the same plate using Dotmatics' Studies Software. The normalized averages (fold change over untreated) of 3 replicate wells for each compound concentration were used to create dose-responses curves and EC_{50} values were calculated using non-linear regression curve fit in the Dotmatics' Studies Software. For EC_{50} of >10 μM, the percent inhibition at 10 μM is provided.

Table 8 shows the activity of representative compounds of Formula I as provided herein.

TABLE 8

Compound	EC_{50} (μM)
1	0.135
3	0.103
4	0.068
6	>10 (45.6%)
10	>10 (39.6%)
14	0.035
16	1.266
69	0.394

TABLE 8-continued

Compound	EC_{50} (μM)
71	>10 (33.4%)
72	0.096
73	0.169
75	0.148
76	0.087
77	0.146
78	0.108
81	0.104
82	0.156
83	0.067
84	0.148
85	0.097
86	>10 (14.6%)
87	0.081
89	0.137
90	0.096
91	>10 (17.3%)
92	>10 (16.7%)
96	0.677
110	0.286
111	0.280
112	0.546
113	2.113
114	0.735
115	0.605
116	0.830
118	0.821
119	1.410
120	2.133
121	1.083
188	>10 (12.4%)
248	7.922
262	0.043
263	0.134
264	>10 (11.7%)
265	2.563
266	0.697
267	0.590
268	0.073
269	0.396
270	>10 (11.4%)
271	0.064
272	2.543
273	0.515
274	0.195
275	0.431
276	0.336
277	0.245
278	0.211
279	1.202
280	0.909
281	0.486
282	1.937
283	0.782
284	2.338
285	1.473
286	>10 (16.4%)
287	2.347
288	0.532
289	>10 (14.3%)
290	1.056
291	>10 (49.6%)
292	2.216
293	7.768
294	>10 (41.3%)
295	4.465
296	1.964
297	0.447
298	1.340
299	1.208
300	0.511
301	4.807
302	0.901
303	0.817
304	0.150
305	5.510
306	0.282
307	7.150

TABLE 8-continued

Compound	EC_{50} (μM)
308	>10 (27.6%)
309	0.014
310	0.294
311	0.076
312	>10 (36.5%)
313	0.105
314	0.045
315	1.822
316	1.082
317	0.174
318	0.073
320	0.069
324	0.068
325	1.304
326	>10 (47.2%)
327	0.058
328	>10 (34.5%)
329	0.212
330	0.020
331	0.096
332	0.291
333	0.061
334	0.063
335	0.111
336	>10 (38.4%)
338	0.643
340	0.413
341	2.372
342	0.948
343	0.446
344	>10 (24.3%)
345	>10 (38.0%)
346	0.965
347	5.220
348	1.457
349	0.145
350	0.100
351	>10 (38.8%)
352	1.322
353	>10 (31.7%)
354	0.346
355	6.191
358	0.145
359	0.127
360	0.094
362	0.782
363	0.387
364	>10 (15.0%)
365	4.799
366	0.173
367	0.211
368	0.272
369	0.295
370	0.379
371	0.394
372	0.504
376	>10 (21.0%)
433	0.052
441	0.057
443	0.371
448	0.059
452	0.220
470	0.387
472	0.243
475	0.140
477	0.077
481	1.021
483	0.315
487	0.367
500	0.675
513	1.353
517	>10 (29.9%)
521	1.991
523	>10 (32.6%)
527	>10 (37.3%)
528	0.103
531	0.153
535	>10 (17.7%)

TABLE 8-continued

Compound	EC_{50} (μM)
537	0.599
547	0.160
554	0.190
561	0.600
579	0.167
643	0.138
699	0.234
700	0.275
704	4.383
707	4.242
711	0.540
713	>10 (37.6%)
718	0.168
737	0.080
741	0.175
743	0.447
758	0.265
760	0.765
767	>10 (33.2%)
773	>10 (30.3%)
784	>10 (37.4%)
785	1.174
791	0.067
795	0.227
803	>10 (27.8%)
822	0.212
826	0.149
831	0.244
851	0.692
883	>10 (14.0%)
885	2.620
900	0.449
921	0.075
932	0.594
939	1.137
946	0.970
952	0.741
960	0.957
963	1.187
964	>10 (19.7%)
965	1.369
966	0.014
967	0.079
968	>10 (24.1%)
969	0.935
970	1.239
971	0.866
972	0.754
973	0.134
974	>10 (49.6%)
975	0.138
976	1.174
977	0.136
978	0.722
979	1.032
980	>10 (40.3%)
981	0.605
982	0.767
983	0.679
984	1.239
985	>10 (38.0%)
986	0.158
987	>10 (42.0%)
988	>10 (46.5%)
989	4.418
990	0.782
991	2.678
992	2.972
993	1.487
994	0.567
995	1.254
996	1.204
997	0.567
998	0.260
999	0.779
1000	2.957
1001	0.065
1002	>10 (27.5%)

TABLE 8-continued

Compound	EC_{50} (μM)
1003	0.049
1004	5.041
1005	0.072
1006	0.061
1007	0.942
1008	0.318
1009	>10 (22.4%)
1010	0.103
1011	>10 (15.9%)
1012	>10 (10.2%)
1013	2.436
1014	0.695
1015	>10 (9.7%)
1016	2.132
1017	0.097
1018	0.088
1019	6.529
1020	>10 (30.6%)
1021	4.494
1022	0.222
1023	4.671
1024	0.549
1025	>10 (31.4%)
1026	2.255
1029	>10 (31.8%)
1030	2.806
1031	>10 (39.2%)
1071	0.712
1073	>10
1074	>10

Example 20

Representative compounds were screened using the following assay procedure to determine their ability to inhibit IL-6 and therefore demonstrate their anti-inflammatory properties.

Human Peripheral Blood Mononuclear Cells:

Fresh Normal PB MNC (Catalog #PB001, AllCells, Alameda, Calif.) were shipped overnight at 4° C. and resuspended in Roswell Park Memorial Institute (RPMI) 1640 Medium, with GlutaMAX Supplement (Catalog #61870127, ThermoFisher Scientific, Waltham, Mass.) supplemented with 1% Penicillin-Streptomycin (Catalog #15140163, ThermoFisher Scientific, Waltham, Mass.) and 1% fetal bovine serum (FBS) (Catalog #16140089, ThermoFisher Scientific, Waltham, Mass.) assay media.

Compound Screening:

Fresh normal human peripheral blood mononuclear cells (huPBMCs) were resuspended in 1% FBS-RPMI assay media with 1% Penicillin-Streptomycin 1% to a cell concentration of 1×10e6 cells/mL. Each compound was dissolved in DMSO (Catalog #D8418-100 ml, Sigma-Aldrich, St. Louis, Mo.) as a 10 mM stock and used to prepare compound source plates. Serial dilution (1:3, 10-point dose-response curves starting from 10 μM) and compound transfer was performed using the ECHO 550 (Labcyte, Sunnyvale, Calif.) into 384-well white Proxiplate-Plus assay plates (Catalog #6008289, PerkinElmer, Shelton, Conn.) with appropriate DMSO backfill for a final DMSO concentration of 0.25%. huPBMCs were plated at 5000 cells/well in the 384-well Proxiplate-Plus assay plates and incubated at 37° C.-5% CO_2 for 2 hours. 50 ng/mL of Lipopolysaccharides from *Escherichia coli* 0111:B4 (Catalog #L5293-2ML, Sigma-Aldrich, St. Louis, Mo.) was added after 2 hours and cells were incubated for another 22 hours at 37° C.-5% CO_2. After 22 hour incubation, a mixture of anti-IL6 XL665 and anti-IL-6 Cryptate diluted in reconstitution buffer (Catalog

#62IL6PEC, Cisbio Inc., Bedford, Mass.) was added to each well. Following incubation for 3 hours at room temperature, Homogeneous Time-Resolved Fluorescence (HTRF) was measured using the Envision (Perkin Elmer, Shelton, Conn.) at 665 nm and 620 nM. The ratio of fluorescence at 665 nm to 620 nm was used as a readout for IL-6 quantification. All samples were processed in duplicate. Readings were normalized to DMSO treated cells and normalized activities were utilized for EC_{50} calculations. EC_{50} was determined using software generated by Dotmatics Limited (Windhill Bishops Stortford Herts, UK) using the Levenberg-Marquardt 4 parameter fitting procedure with finite different gradients. For EC_{50} of >10 μM, the percent inhibition at 10 μM is provided.

Table 9 shows the activity of representative compounds of Formula I as provided herein.

TABLE 9

Compound	EC_{50} (μM)
1	0.338
3	0.792
4	1.131
6	1.286
10	0.399
14	0.643
16	2.166
69	2.157
71	6.733
72	1.127
73	0.963
75	0.806
76	1.127
77	0.958
78	2.941
81	0.395
82	1.186
83	2.152
84	2.463
85	1.148
86	1.772
87	2.939
89	1.136
90	1.083
91	>10 (40.0%)
92	>10 (33.0%)
96	>10 (5.8%)
110	0.484
112	2.989
113	1.917
114	1.140
115	1.913
116	1.334
118	3.606
119	1.198
120	2.291
121	3.653
188	9.975
248	9.730
262	1.092
263	0.451
264	>10 (4.0%)
265	2.997
266	1.933
267	9.407
268	8.174
269	3.389
270	9.975
271	3.084
272	3.095
273	0.842
274	3.223
275	1.142
276	2.920
277	>10 (4.0%)
278	3.988
279	>10 14.2%)

TABLE 9-continued

Compound	EC_{50} (μM)
280	>10 (11.6%)
281	>10 (0%)
282	>10 (2.4%)
283	5.452
284	1.182
285	2.273
286	1.227
287	9.578
288	1.236
289	3.195
290	4.782
291	9.827
292	1.116
293	1.170
294	6.228
295	>10 (5.9%)
296	1.575
297	1.170
298	5.533
299	4.528
300	2.739
301	0.393
302	7.698
303	5.235
304	1.144
305	1.144
306	2.517
307	>10 (4.3%)
308	9.229
309	>10 (4.5%)
310	1.167
311	0.396
312	>10 (3.9%)
313	1.009
314	1.273
315	0.819
316	0.395
317	1.897
318	1.031
320	1.264
324	0.321
325	0.357
326	0.380
327	0.947
328	0.398
329	1.158
330	1.157
331	0.882
332	1.066
333	0.790
334	0.263
335	0.401
336	0.569
338	4.458
340	0.562
341	>10 (46.1%)
342	4.167
343	>10 (47.4%)
344	9.133
345	4.167
346	9.438
347	>10 (4.5%)
348	>10 (19.0%)
349	0.307
350	0.578
351	3.009
352	5.026
353	>10 (39.9%)
354	7.000
355	9.133
358	0.613
359	1.026
360	1.167
362	9.153
363	1.223
364	>10 (5.8%)
365	0.526
366	1.120

TABLE 9-continued

Compound	EC_{50} (μM)
367	1.153
368	1.186
369	1.128
370	3.708
371	1.209
372	3.656
376	>10 (11.8%)
433	0.411
441	3.351
443	3.289
448	2.185
452	2.973
468	5.776
470	3.550
472	5.409
475	2.562
477	2.994
481	1.143
483	9.616
487	3.299
500	>10 (4.0%)
513	>10 (14.5%)
517	9.068
521	3.248
523	0.201
527	9.975
528	1.785
531	0.698
535	>10 (3.1%)
537	1.243
547	1.119
554	0.439
561	0.634
579	1.017
643	0.129
699	0.410
700	0.380
704	>10 (4.8%)
707	0.446
711	1.080
713	3.633
718	0.406
731	1.179
737	1.179
741	0.380
743	1.127
758	2.871
760	1.245
767	3.817
773	3.481
784	>10 (3.7%)
785	9.147
791	0.350
795	1.218
798	1.268
803	3.317
822	3.260
826	3.294
831	0.812
839	3.276
851	>10 (2.9%)
883	>10 (9.1%)
885	>10 (7.0%)
888	3.944
900	9.862
921	>10 (9.9%)
932	>10 (7.5%)
939	>10 (3.6%)
946	>10 (18.2%)
952	>10 (10.1%)
959	>10 (6.1%)
960	>10 (8.2%)
962	>10 (9.6%)
963	>10 (8.2%)
964	>10 (6.8%)
965	3.263
967	1.130
968	9.238

TABLE 9-continued

Compound	EC_{50} (μM)
969	9.123
970	1.132
971	1.220
972	1.134
973	0.395
974	>10 (45.9%)
975	0.425
977	0.404
978	3.364
979	4.303
980	3.680
981	1.104
982	2.787
983	>10 (9.1%)
984	8.760
985	3.891
986	>10 (13.4%)
987	>10 (6.5%)
988	>10 (8.8%)
989	>10 (12.5%)
990	>10 (0%)
991	3.236
992	>10 (2.6%)
993	8.836
994	>10 (31.8%)
995	8.930
996	>10 (10.6%)
997	>10 (28.6%)
998	7.082
999	>10 (30.3%)
1000	8.724
1001	>10 (49.7%)
1002	>10 (5.9%)
1003	1.146
1004	1.177
1005	2.890
1006	1.128
1007	1.262
1008	7.591
1009	1.840
1010	1.170
1011	>10 (15.3%)
1012	3.122
1013	6.824
1014	3.201
1015	3.119
1016	>10 (5.4%)
1017	0.655
1018	0.441
1019	8.973
1020	1.181
1021	>10 (5.1%)
1022	3.288
1023	>10 (20.7%)
1024	>10 (33.1%)
1025	>10 (13.6%)
1026	9.523
1027	>10 (0%)
1028	1.934
1029	>10 (7.3%)
1030	>10 (7.7%)
1031	>10 (2.0%)
1032	3.323
1034	3.325
1035	1.027
1037	7.521
1040	1.177
1041	0.941
1047	>10 (4.5%)
1048	>10 (4.3%)
1049	>10 (10.4%)
1057	3.202
1061	0.947
1064	3.505
1067	8.940
1068	3.404
1070	6.470
1071	>10 (8.8%)

TABLE 9-continued

Compound	EC_{50} (μM)
1073	>10 (3.3%)
1074	>10 (5.6%)
1075	3.266
1076	>10 (3.0%)
1077	3.167
1078	3.242
1079	1.214
1080	1.073
1081	1.097
1082	2.929
1083	8.734
1084	0.752
1085	0.453
1086	0.394
1087	0.470
1088	5.978
1090	0.484

Example 21

Representative compounds were screened using the cell-based assay procedure for secreted cytokines in a Lipopolysaccharide-stimulated mouse glial cell line described below.

BV-2 cells (mouse microglial cells) were cultured in 1:1 DMEM medium supplemented with 10% FBS, and 1% penicillin/streptomycin.

Compound Screening:

BV-2 cells are plated at 35,000 cells/well in a volume of 100 ul for at least 4 hours before compounds are added. DMSO-resuspended compounds were first dispensed in a 96 well plate and serial diluted from 10 μM to 4.6 nM final concentration in medium. Compounds were added to cells overnight. Two hundred fifty ng per milliliter of lipopolysaccharide (*Escherichia coli* O55:B5, SIGMA) was added for 5 h. Supernatant is removed and saved for further cytokine detection. The original plates with seeded cells were tested for cytotoxicity by measure of adenosine triphosphate (ATP) release by adding CellTiter-Glo® diluted 1:4 in distilled water (G7573, Promega) and transferring lysed cells to a completely black 96-well plate to be read with the Cytation3. Supernatant was then diluted 1:2 with a diluent from V-PLEX cytokine Kit and directly tested for the secreted cytokines TNFα, IL-6 and KC-GRO using electrochemiluminescence (Meso Scale Discovery). The standard curve for each cytokine was used to convert the electrochemiluminescent signal into pg of protein per mL. The signal was used to plot, draw the curve fitting, and determine each compounds EC_{50} in Prism (GraphPad).

Table 10 shows the activity of representative compounds of Formula I as provided herein.

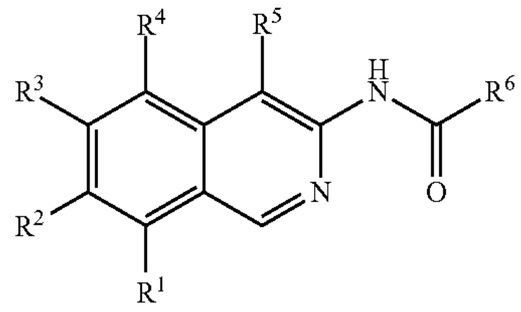
TABLE 10

Compound	TNFα EC_{50} (μM)	IL-6 EC_{50} (μM)	KC/Gro EC_{50} (μM)
73	0.023	0.080	ND
81	>10	0.030	ND
83	ND	0.006	ND
262	3.2	1.5	ND
278	>10	0.217	ND
324	0.033	0.020	ND
338	0.724	0.144	ND
468	2.1	0.023	ND
500	1.2	0.034	0.007
966	0.060	0.022	0.071
1006	0.024	0.011	0.027
1017	0.029	0.024	0.022
1020	0.597	0.087	0.708
1064	0.030	0.006	0.014
1070	ND	0.014	ND
1076	1.8	0.008	0.291

ND = Not Determined

What is claimed is:

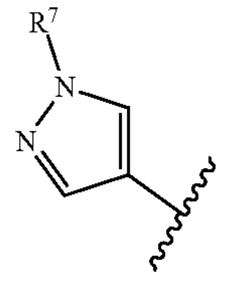
1. A compound, or a pharmaceutically acceptable salt thereof, of Formula I:



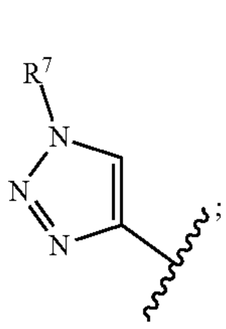
wherein:

R^1, R^2, R^4, and R^5 are H;

R^3 is selected from the group consisting of



and



R^6 is selected from the group consisting of -heterocyclyl optionally substituted with 1-3 R^{36};

R^7 is selected from the group consisting of H, unsubstituted —(C_{1-5} alkyl), and -carbocyclyl;

each R^{36} is independently selected from the group consisting of halide, unsubstituted —(C_{1-6} alkyl), unsubstituted —(C_{2-6} alkenyl), unsubstituted —(C_{2-6} alkynyl), unsubstituted —(C_{1-6} haloalkyl), —(C_{1-4} alkylene)OR^{42}, -heterocyclyl optionally substituted with 1-2 R^{43}, and —$SO_2(R^{52})$; wherein —(C_{1-4} alkylene) is optionally substituted with one or more halides;

each R^{42} is independently selected from the group consisting of H and unsubstituted —(C_{1-5} alkyl);

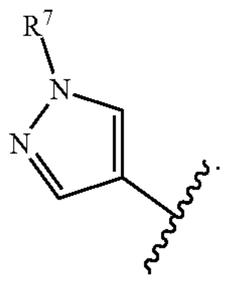
each R^{43} is independently selected from the group consisting of halide and unsubstituted —(C_{1-5} alkyl); and

R^{52} is selected from the group consisting of unsubstituted —(C_{1-5} alkyl) and -aryl optionally substituted with one or more halides;

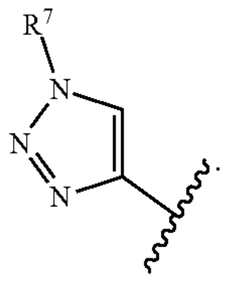
wherein one or more H are optionally replaced by D;

wherein each heterocyclyl is independently a nonaromatic cyclic ring system comprising at least one heteroatom in the ring system backbone.

2. The compound of claim **1**, wherein R^3 is



3. The compound of claim **1**, wherein R^3 is



4. The compound of claim **2**, wherein R^7 is —(C_{1-3} alkyl).

5. The compound of claim **3**, wherein R^7 is —(C_{1-3} alkyl).

6. The compound of claim **2**, wherein R^7 is H.

7. The compound of claim **2**, wherein R^7 is Me.

8. The compound of claim **3**, wherein R^7 is Me.

9. The compound of claim **7**, wherein R^6 is selected from the group consisting of piperidinyl, pyrrolidinyl, azepanyl, 7-azaspiro[3.5]nonanyl, and 2-azaspiro[3.3]heptanyl, all optionally substituted with 1-2 R^{36}.

10. The compound of claim **8**, wherein R^6 is selected from the group consisting of piperidinyl, pyrrolidinyl, azepanyl, 7-azaspiro[3.5]nonanyl, and 2-azaspiro[3.3]heptanyl, all optionally substituted with 1-2 R^{36}.

11. The compound of claim **9**, wherein R^6 is a piperidinyl substituted with one —(C_{1-5} alkyl).

12. The compound of claim **9**, wherein R^6 is a piperidinyl substituted with one —(C_{1-4} haloalkyl).

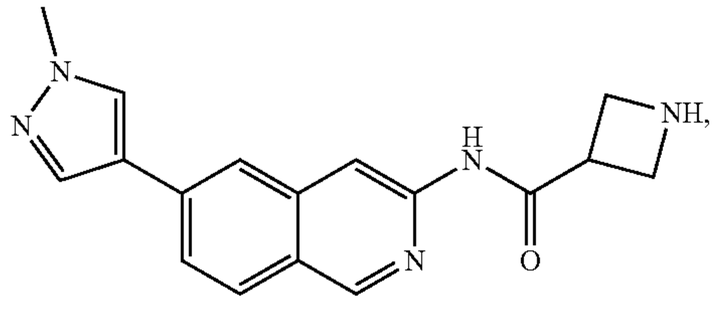
13. The compound of claim **9**, wherein R^6 is a piperidinyl substituted with one —SO_2Me.

14. The compound of claim **10**, wherein R^6 is a piperidinyl substituted with one —(C_{1-5} alkyl).

15. The compound of claim **10**, wherein R^6 is a piperidinyl substituted with one —(C_{1-4} haloalkyl).

16. The compound of claim **10**, wherein R^6 is a piperidinyl substituted with one —SO_2Me.

17. The compound of claim **1**, wherein the compound of Formula I is selected from the group consisting of:



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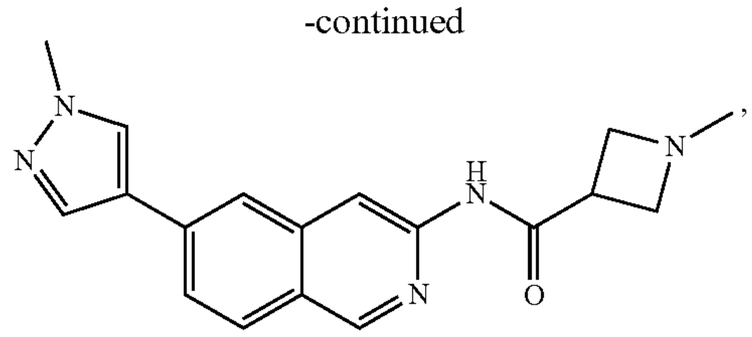

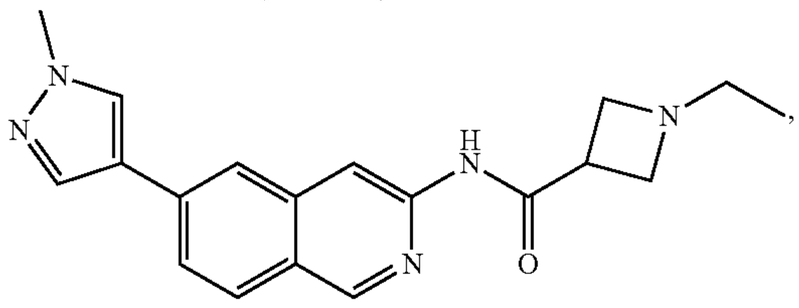

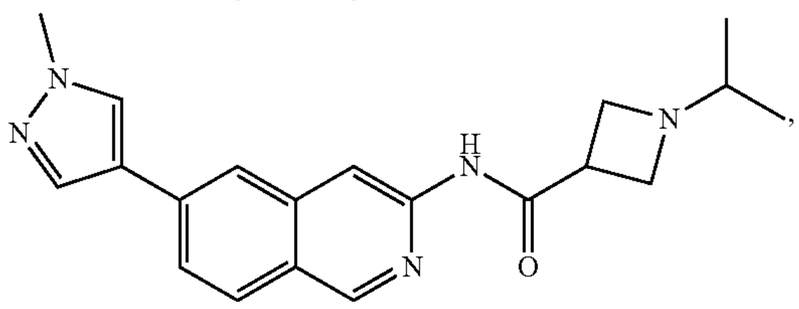

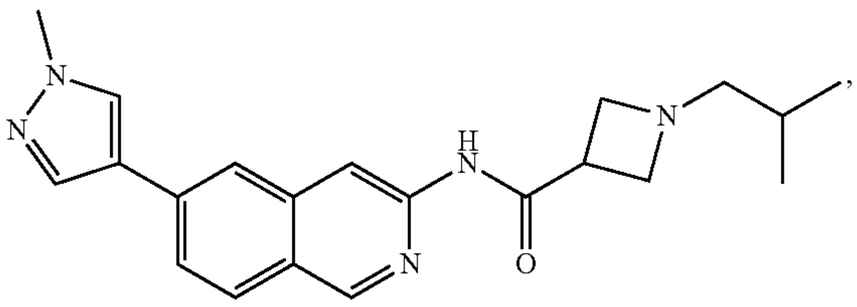

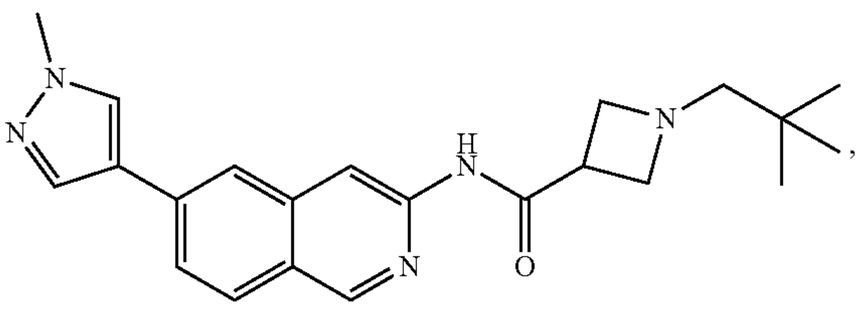

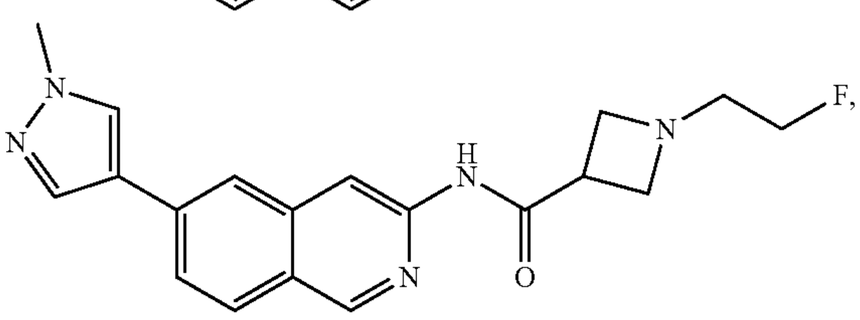

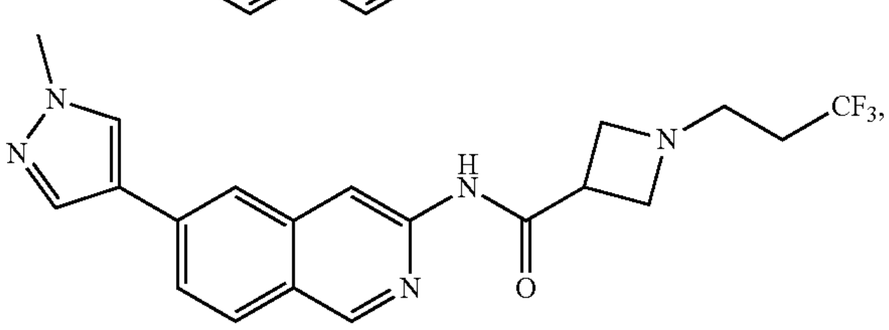

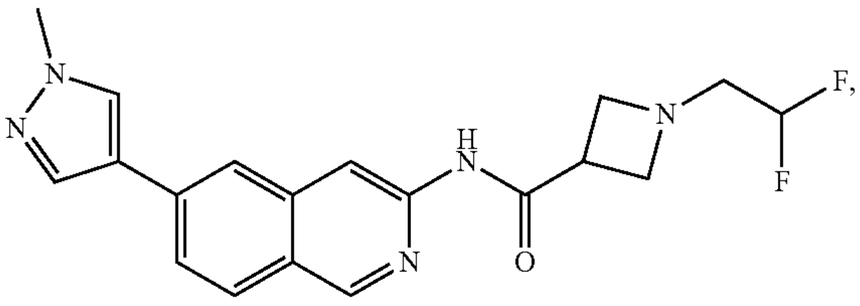

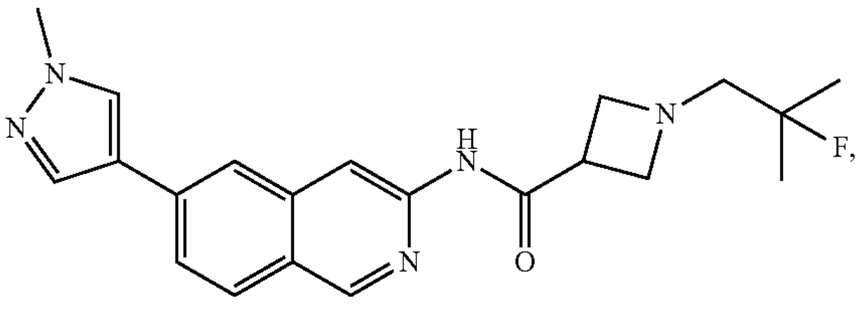

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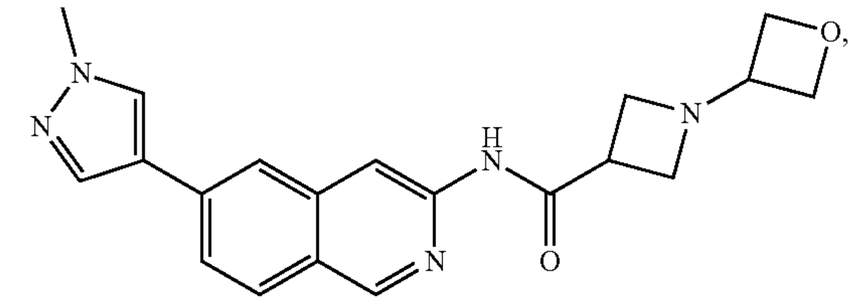

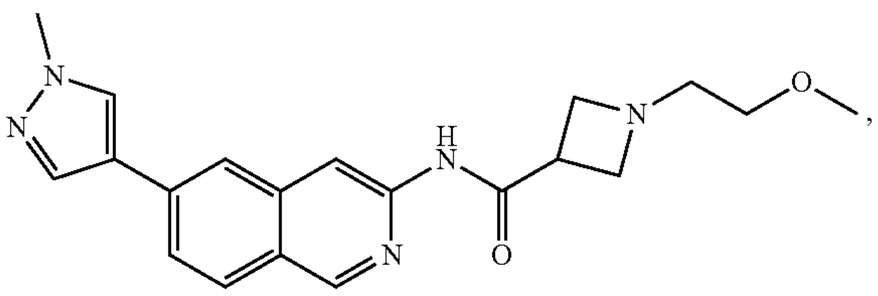

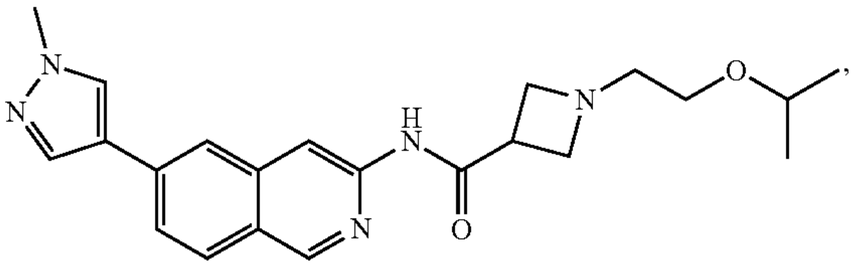

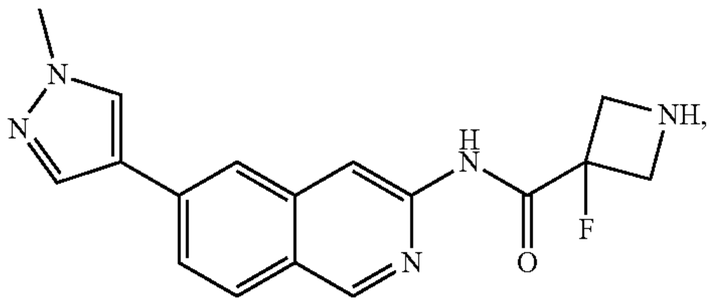

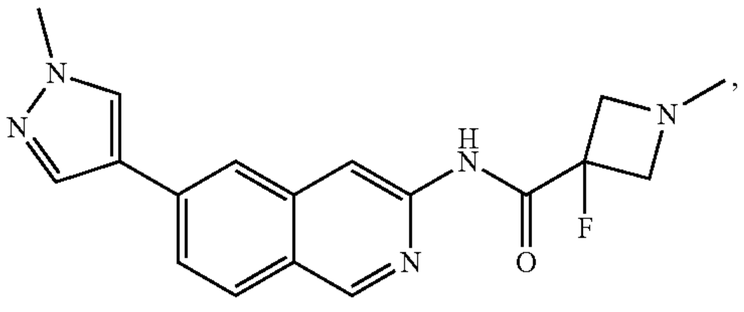

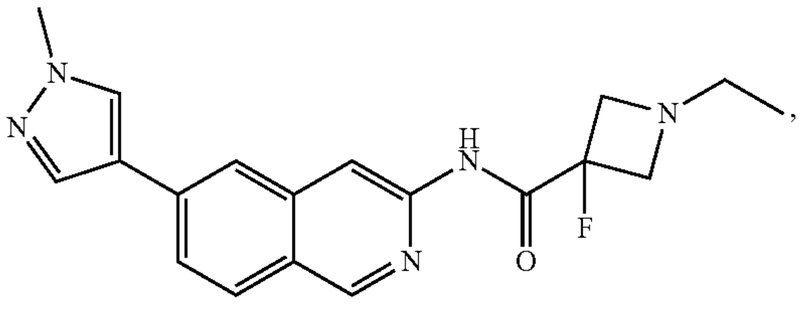

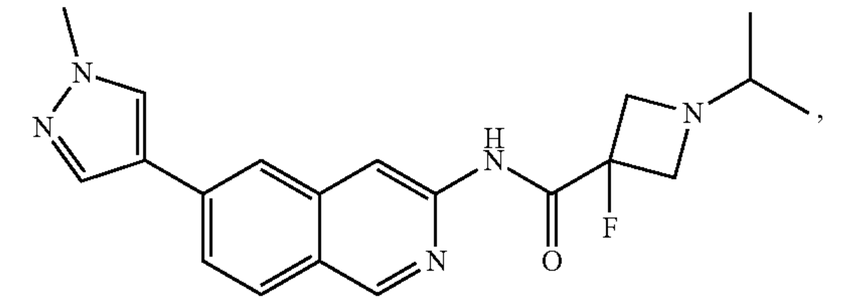

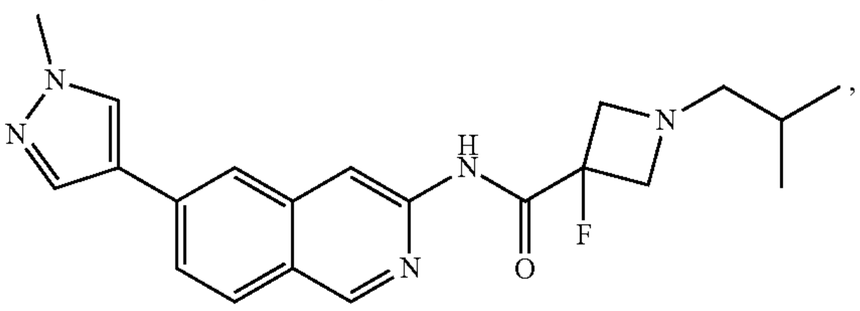

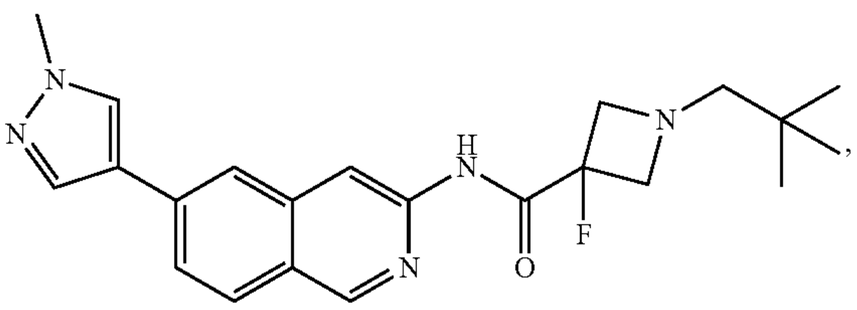

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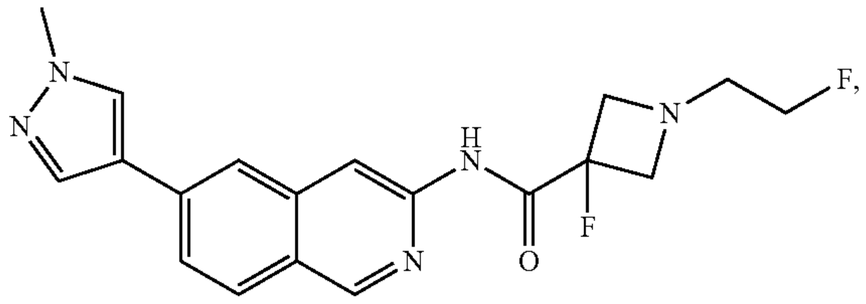

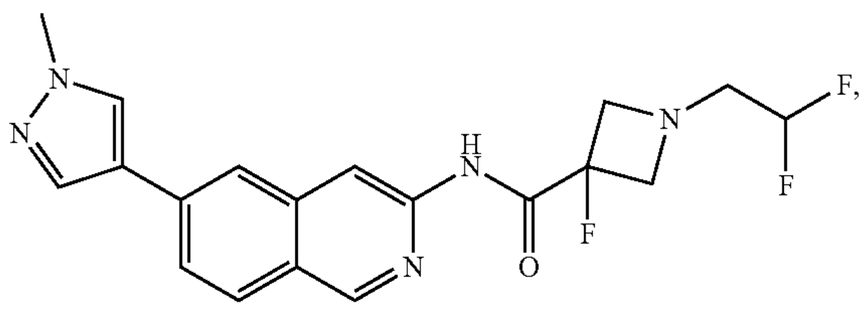

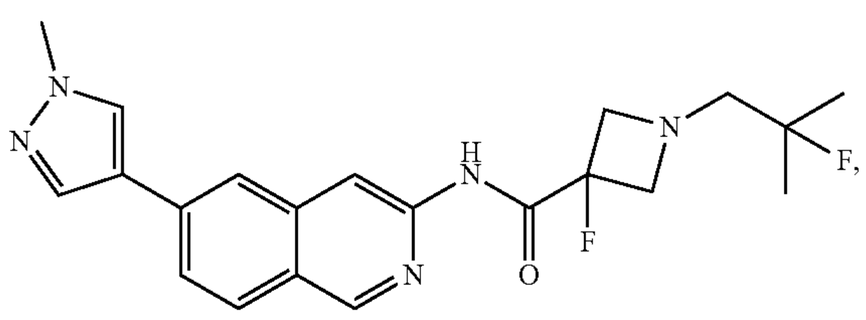

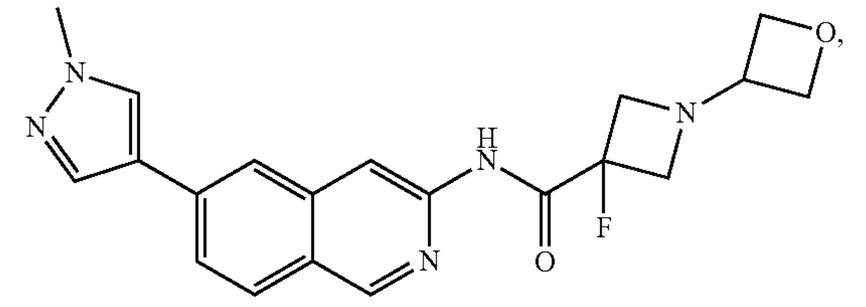

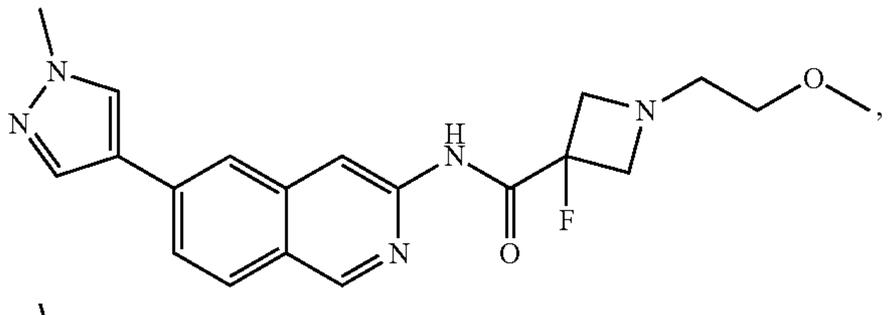

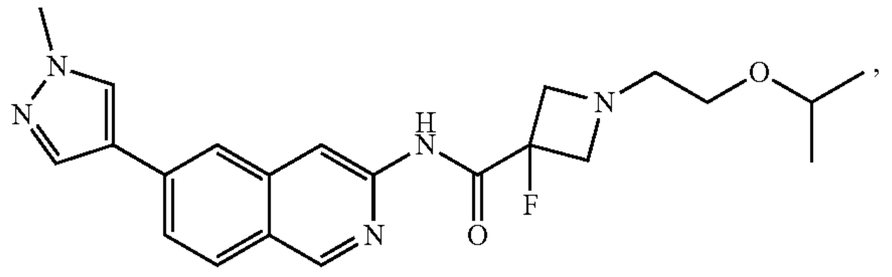

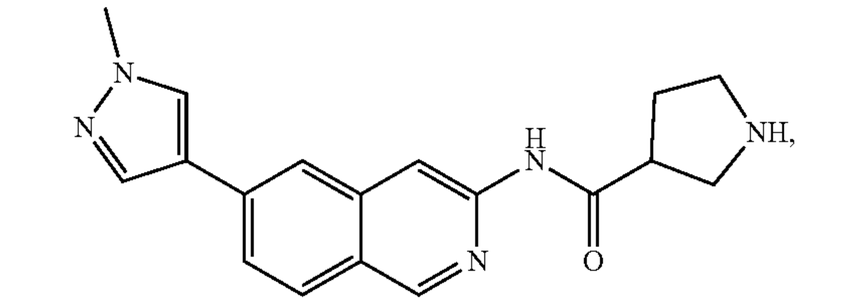

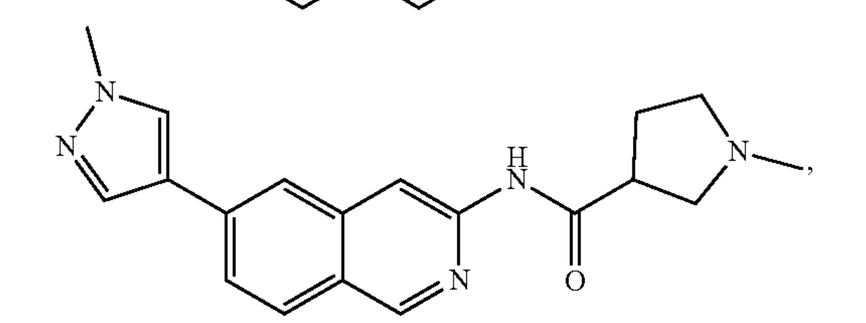

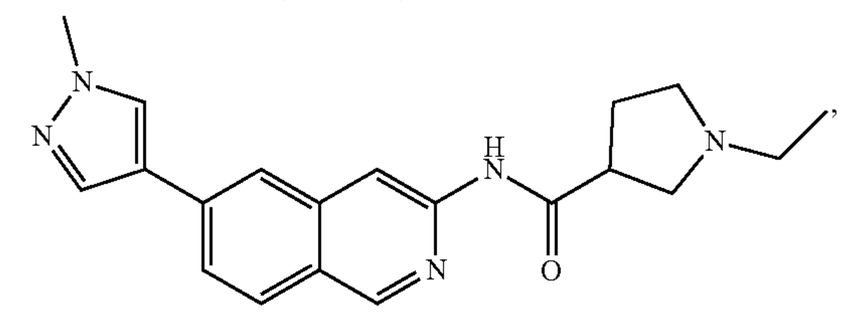

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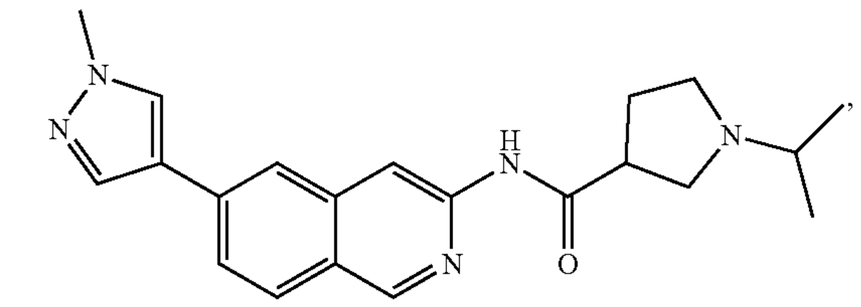

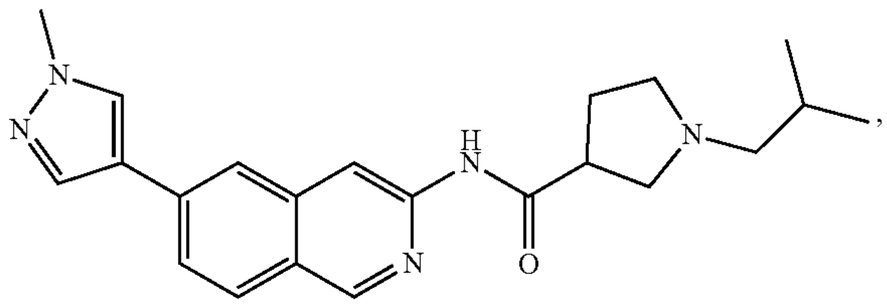

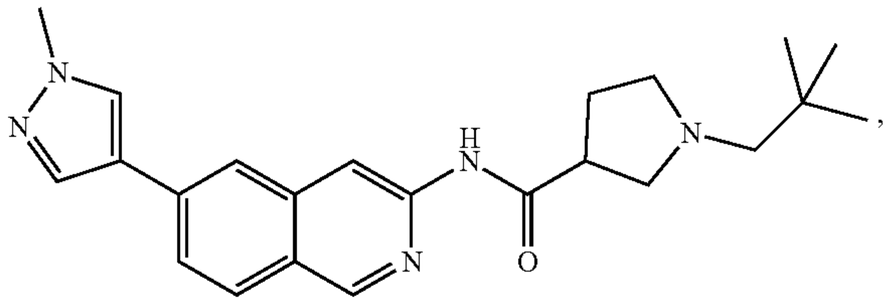

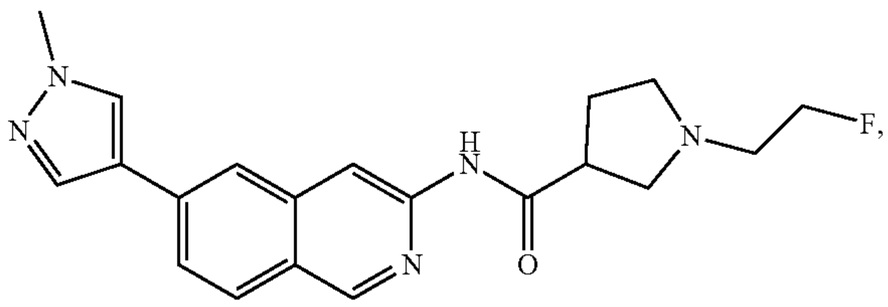

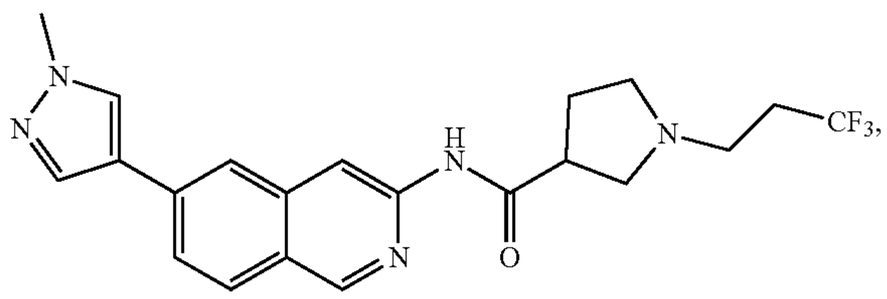

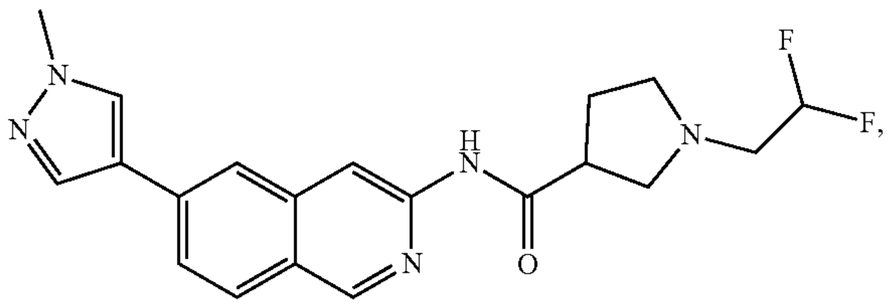

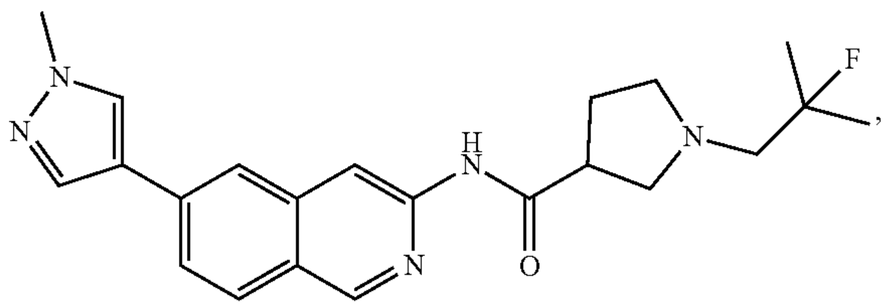

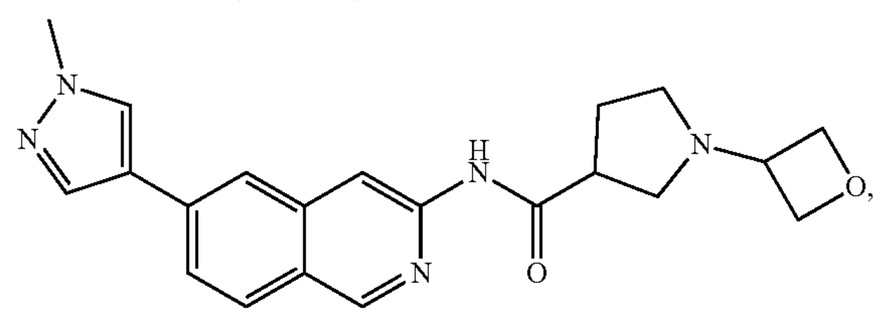

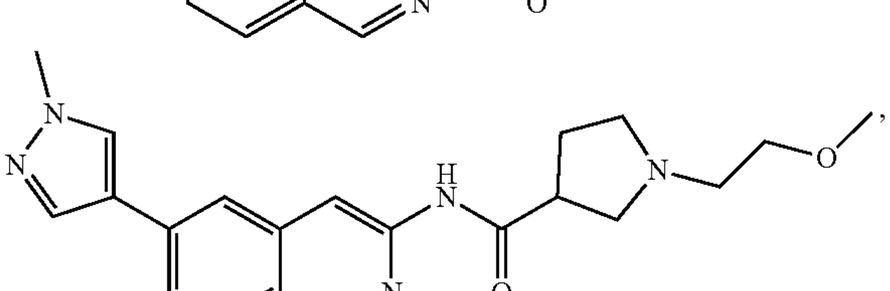

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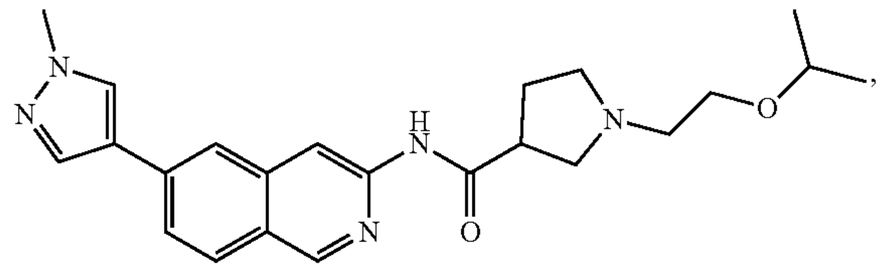

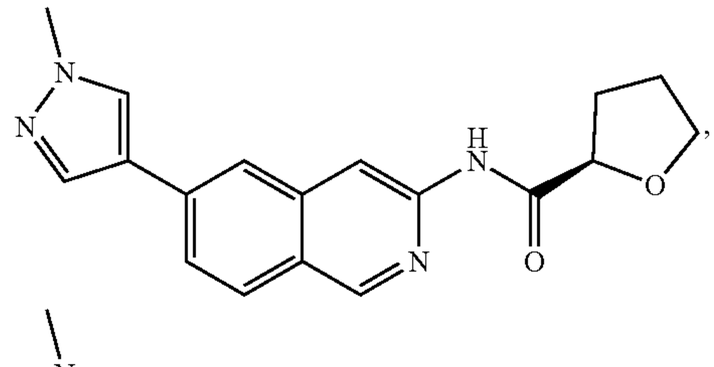

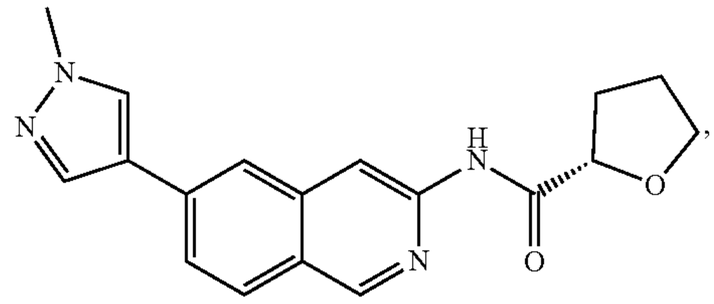

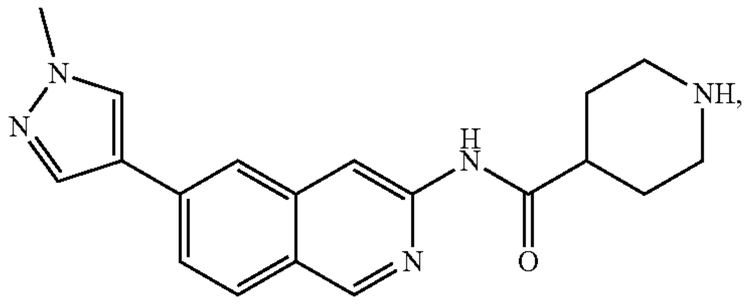

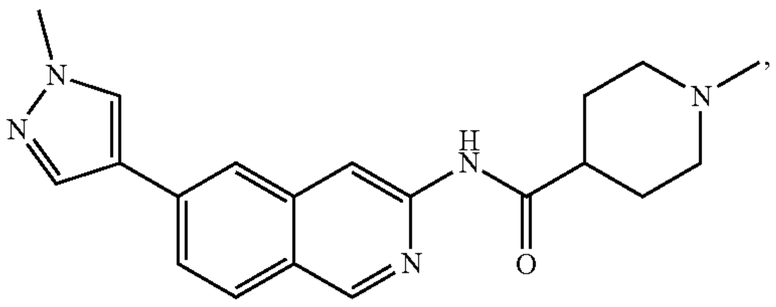

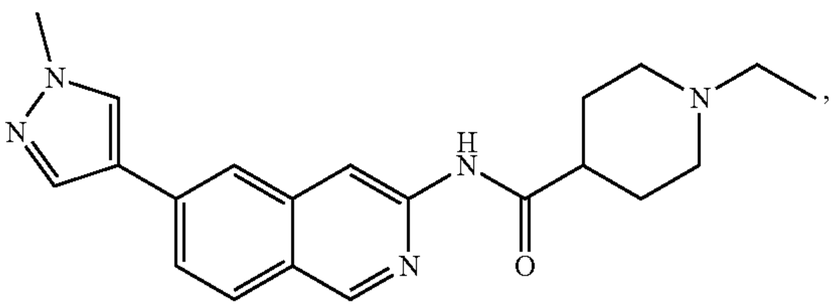

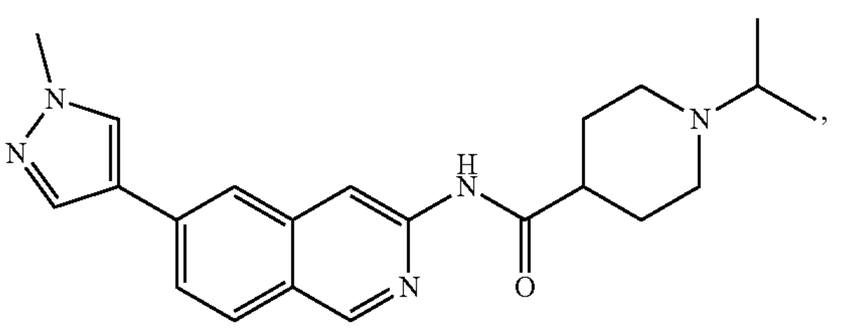

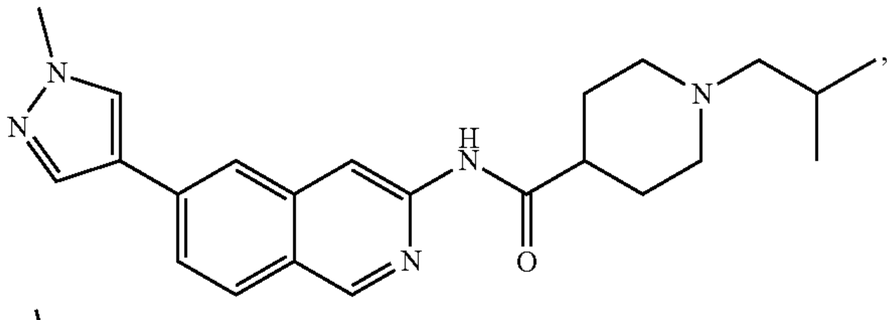

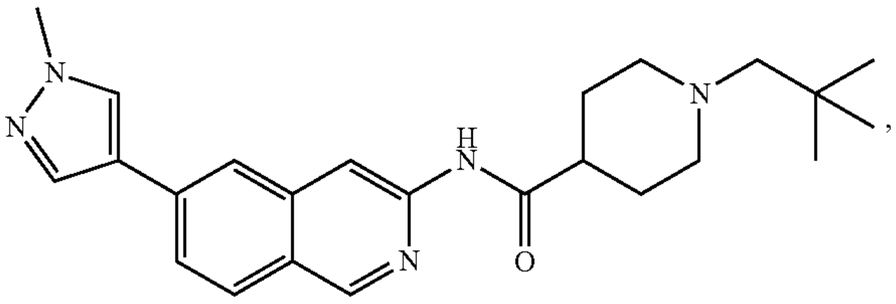

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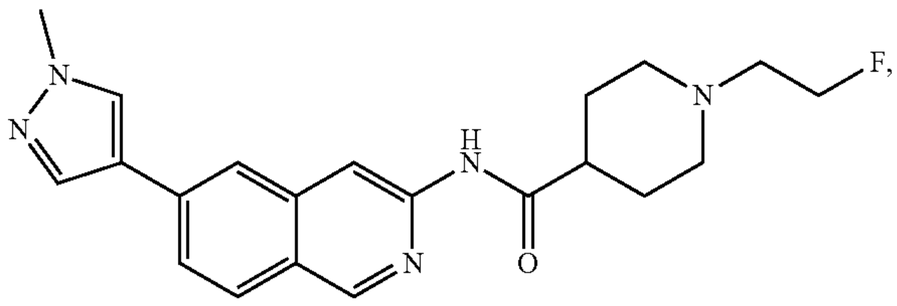

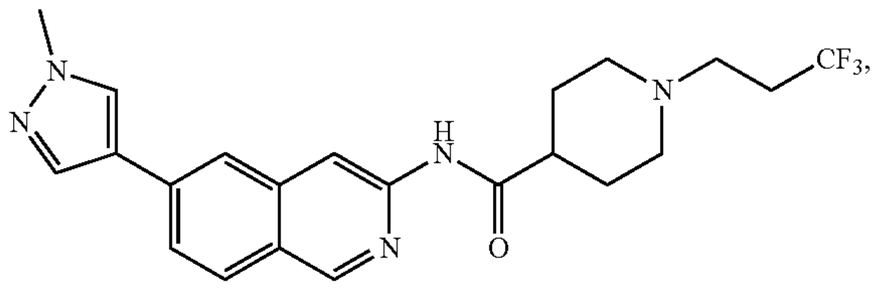

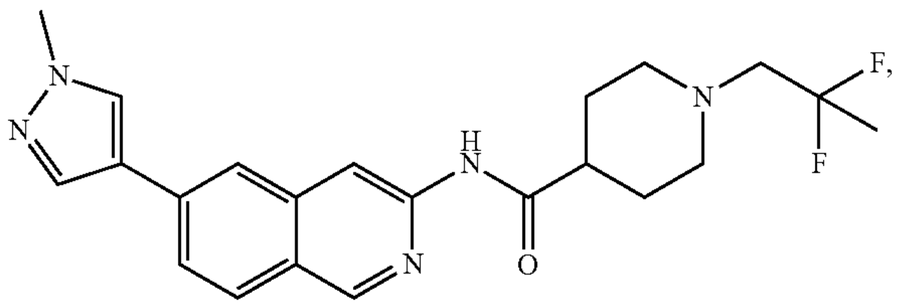

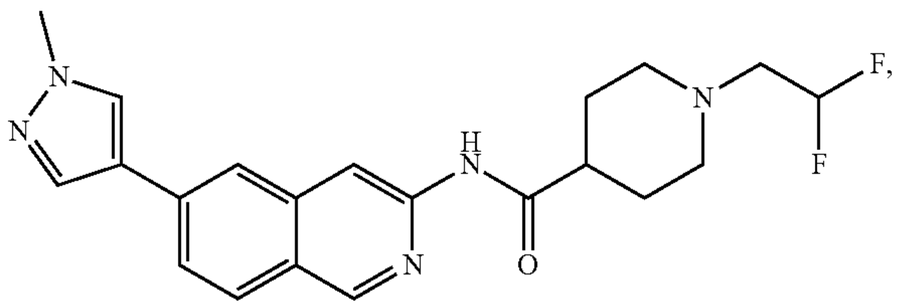

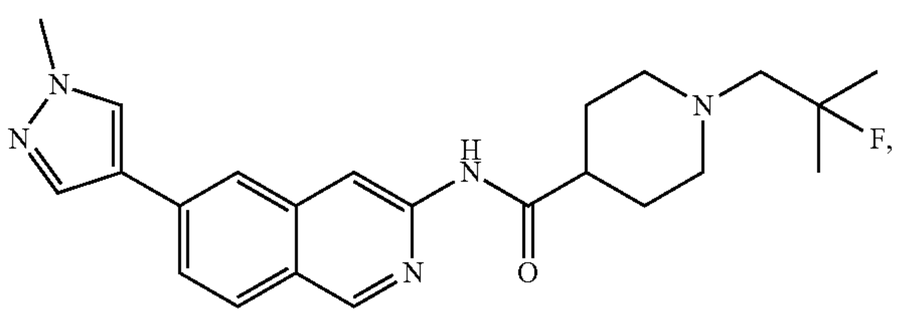

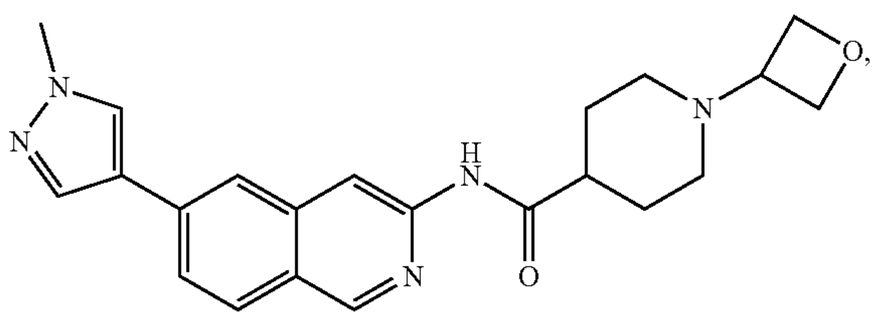

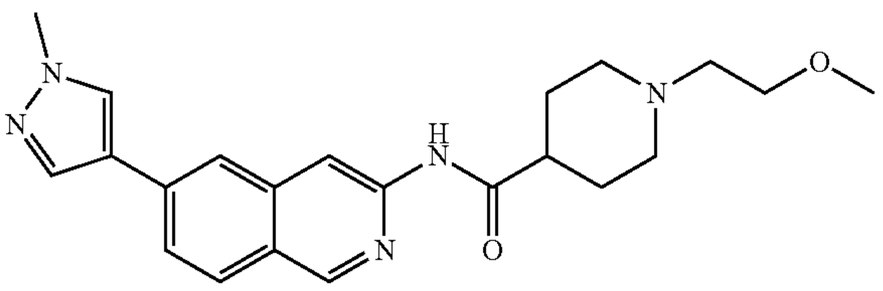

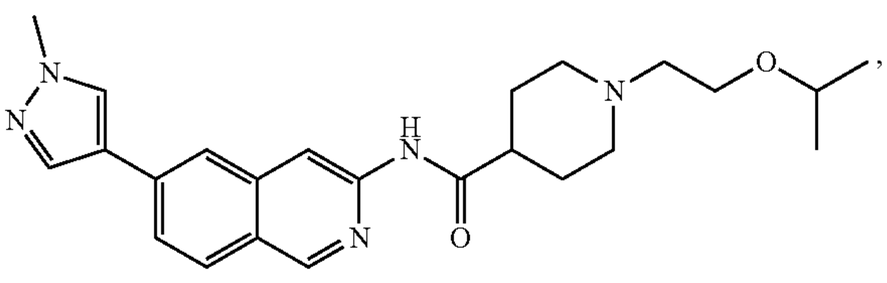

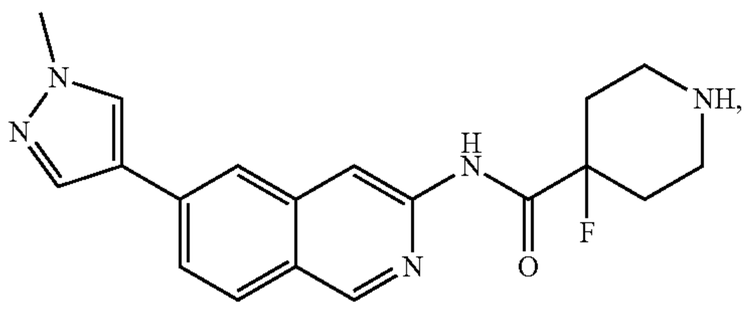

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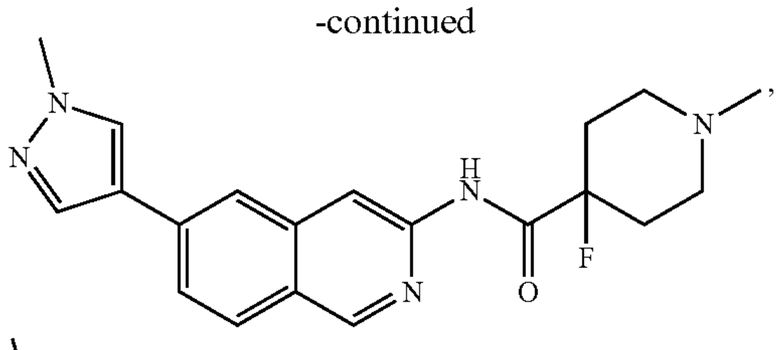

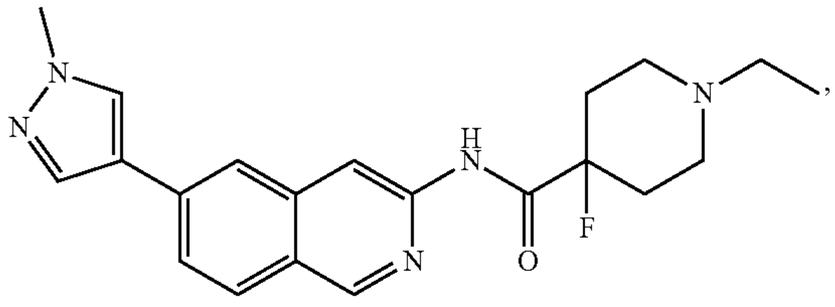

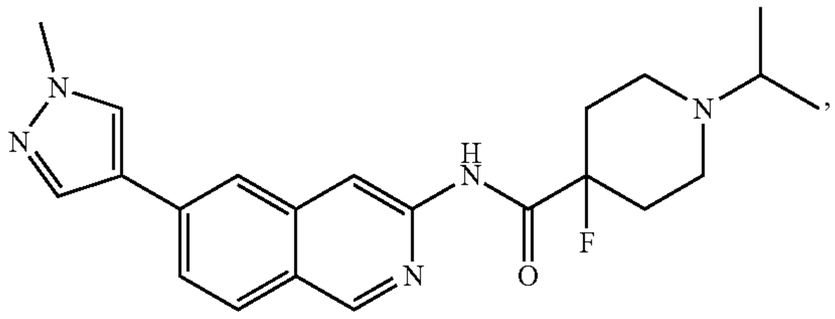

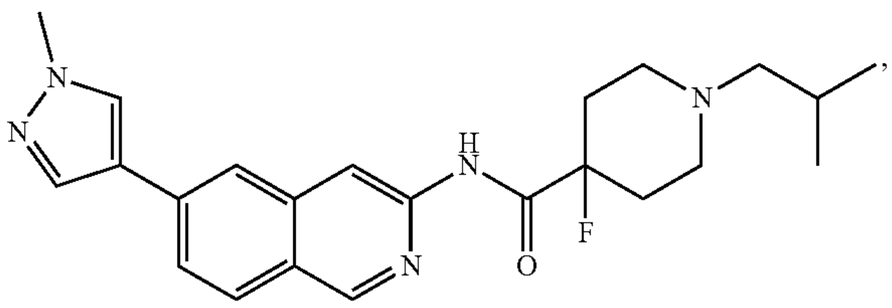

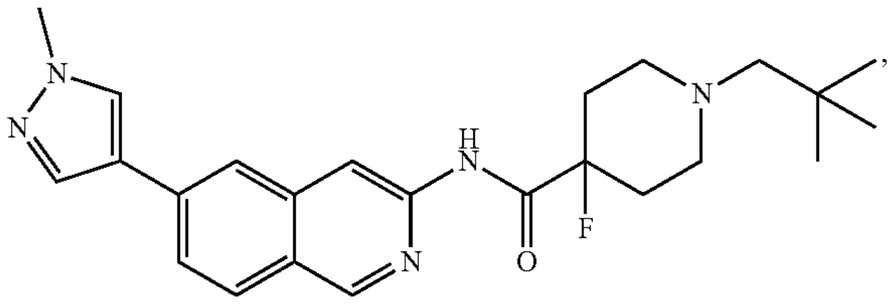

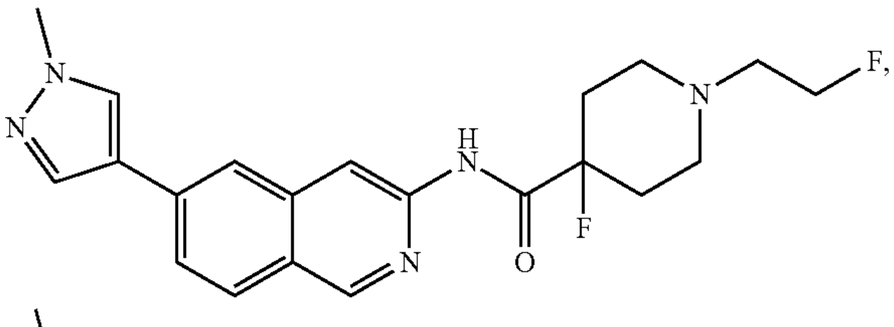

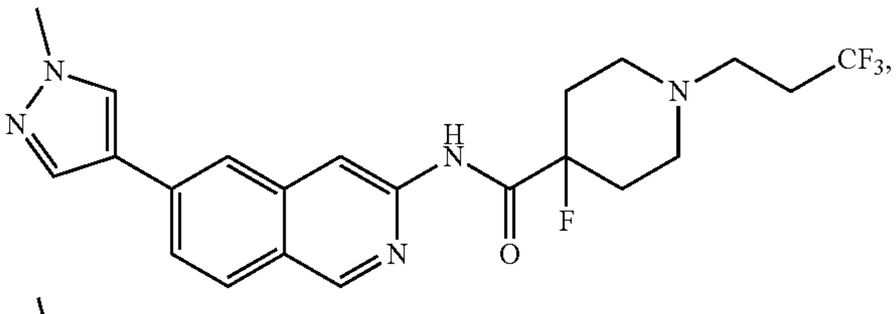

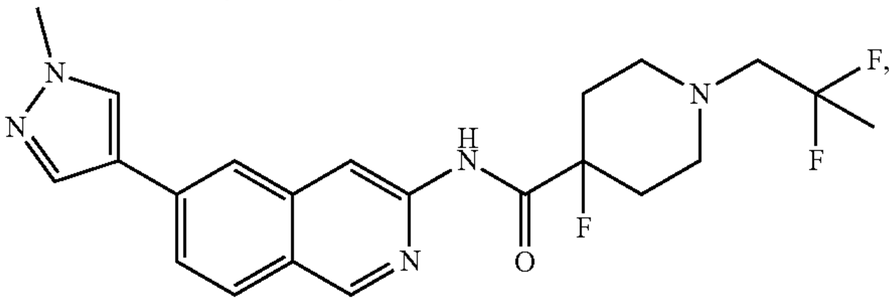

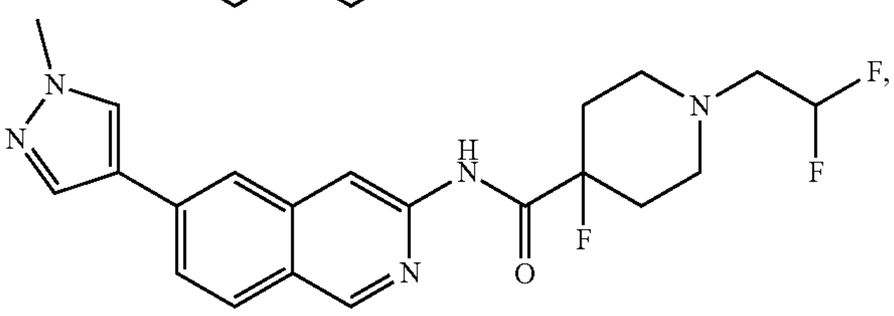

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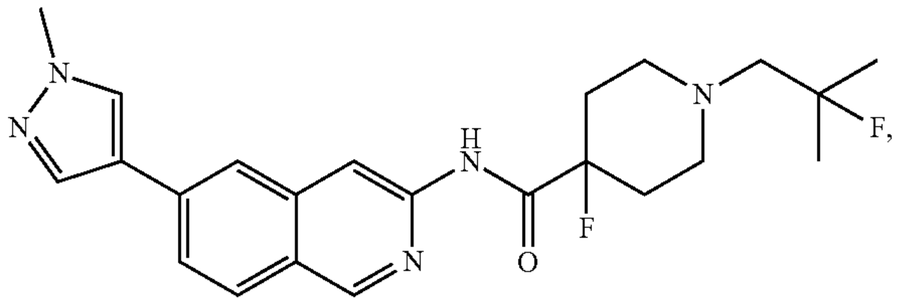

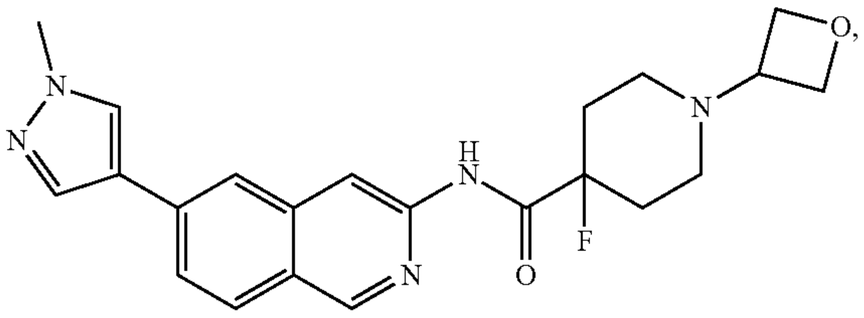

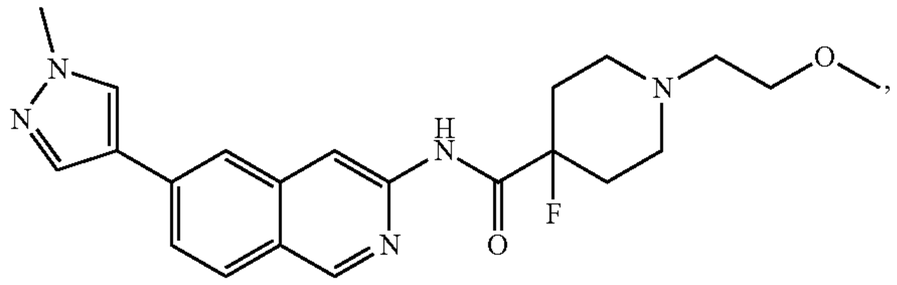

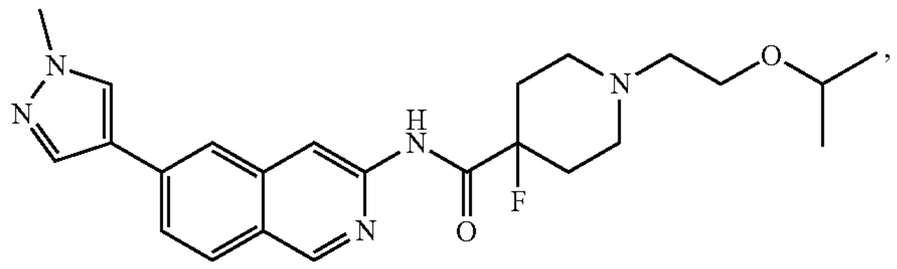

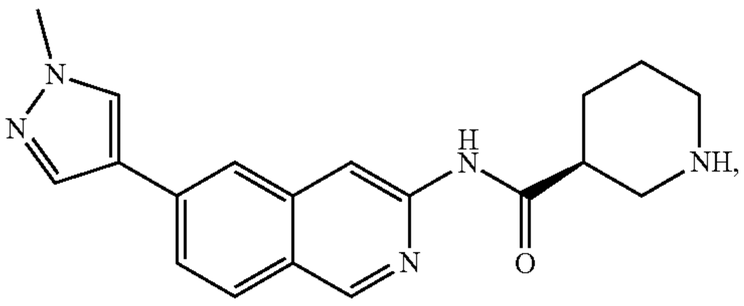

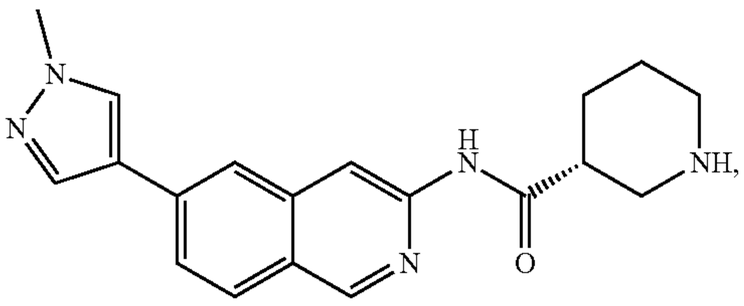

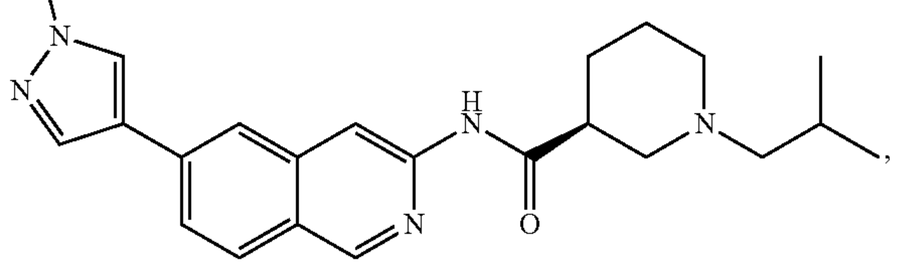

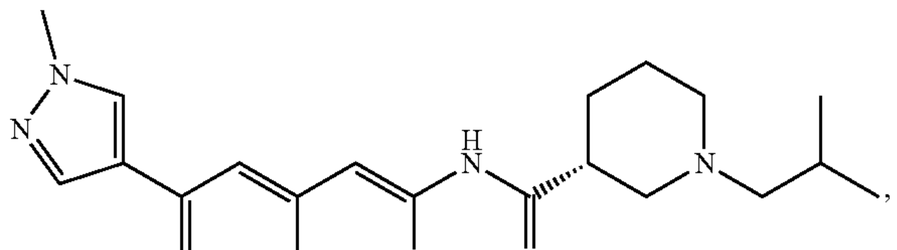

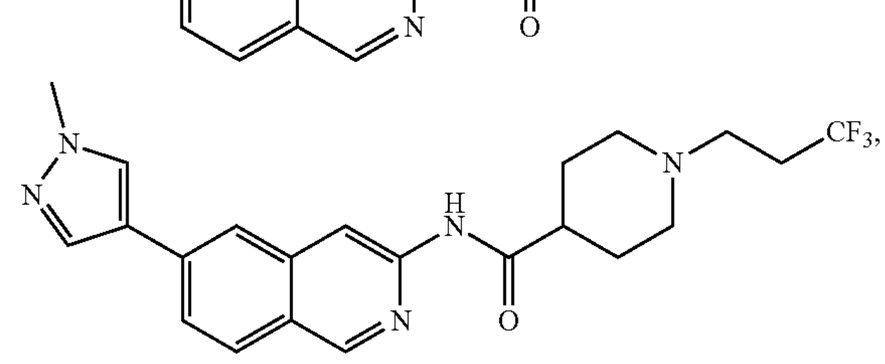

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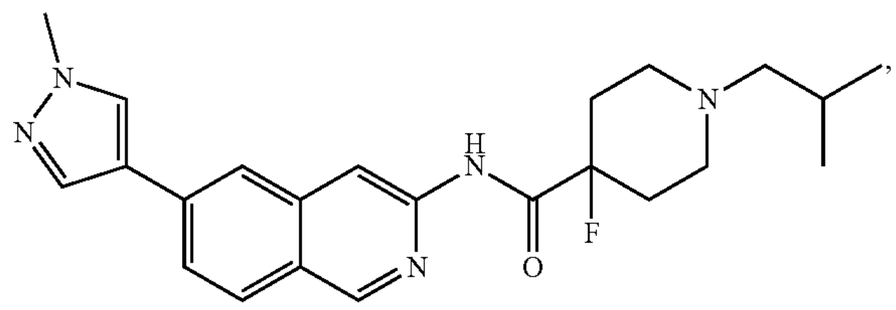

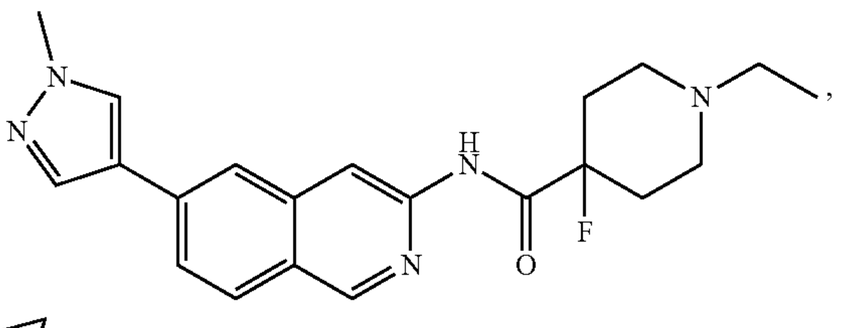

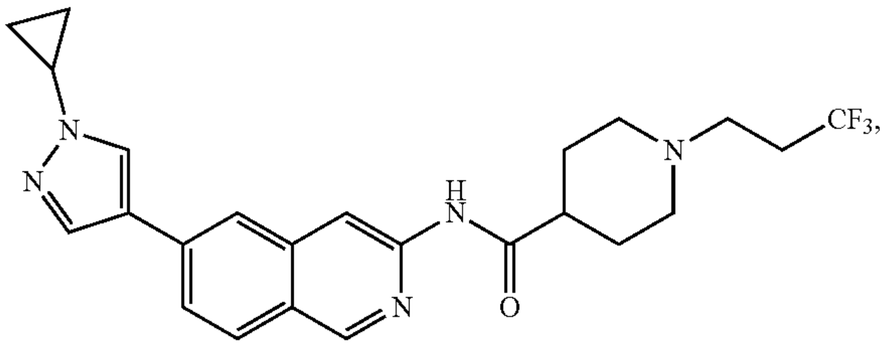

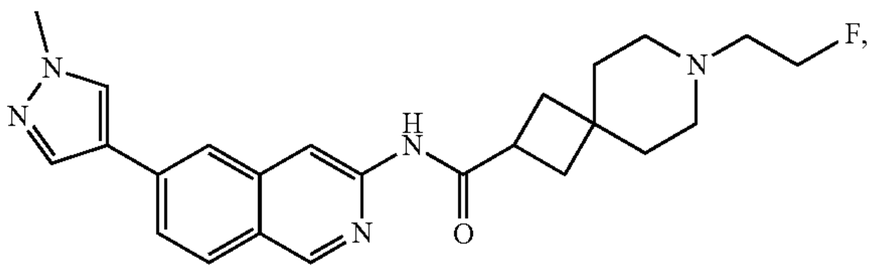

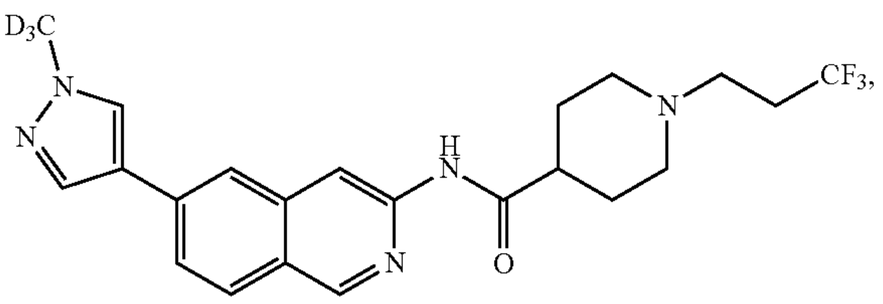

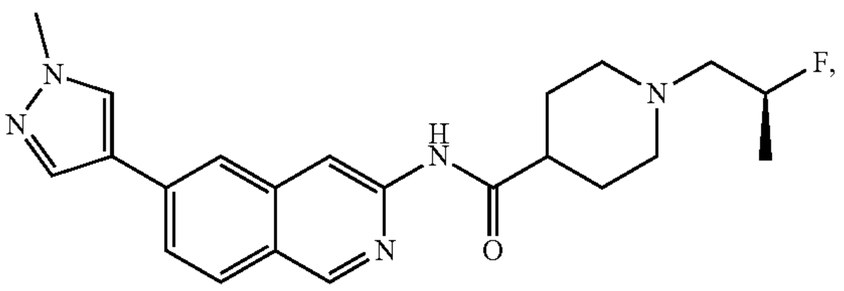

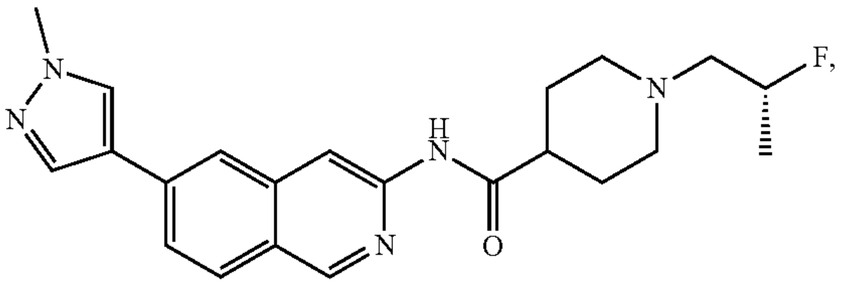

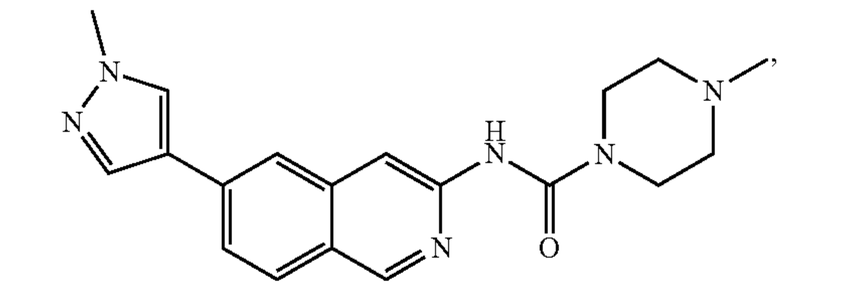

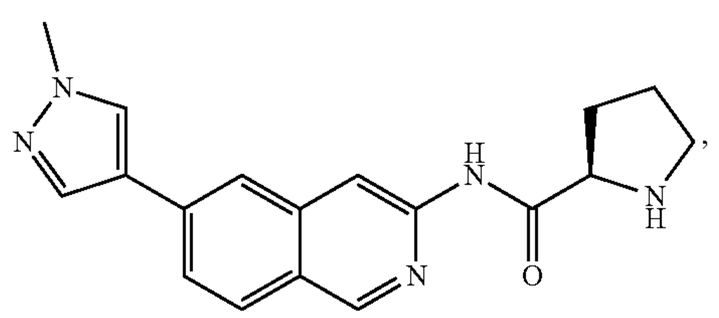

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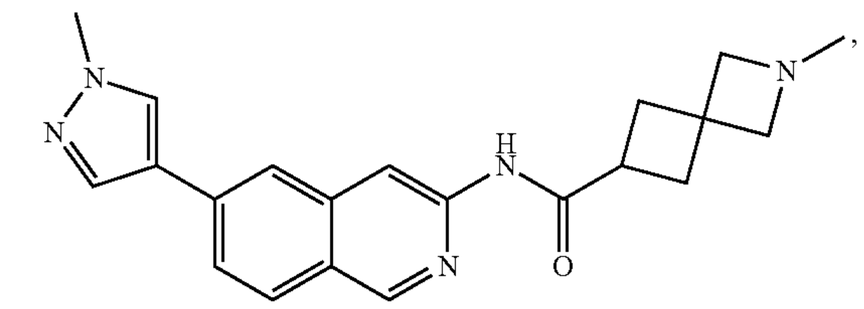

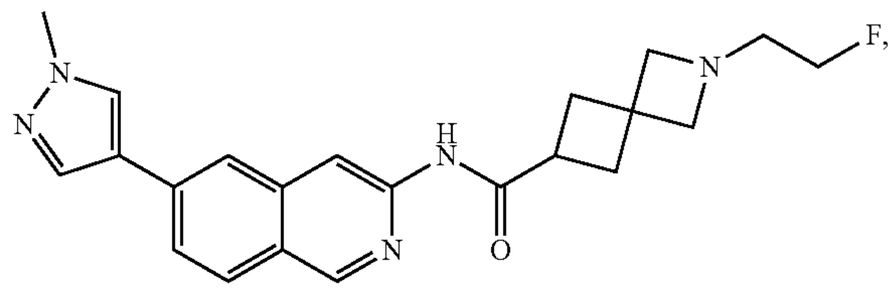

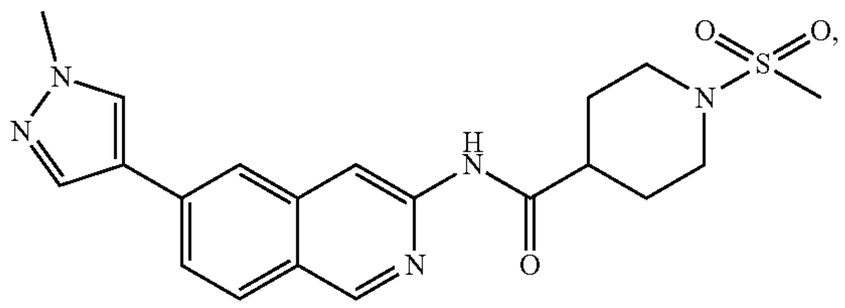

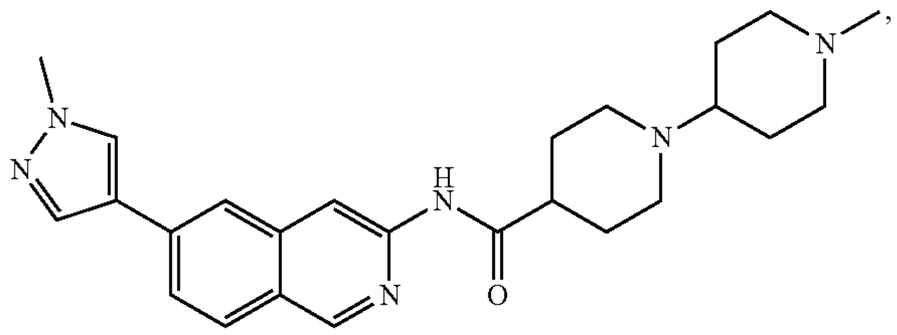

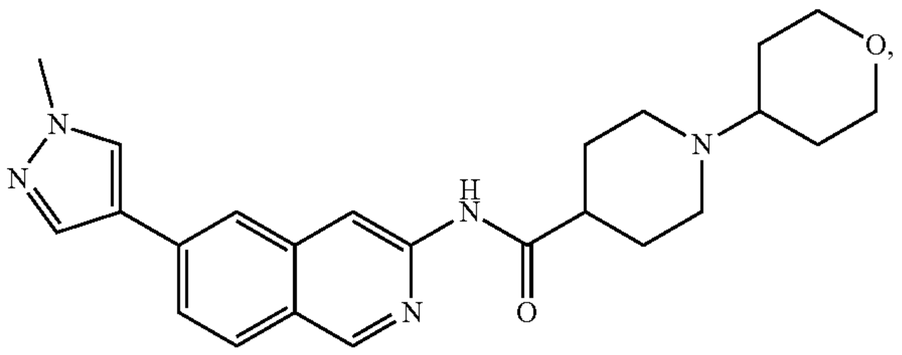

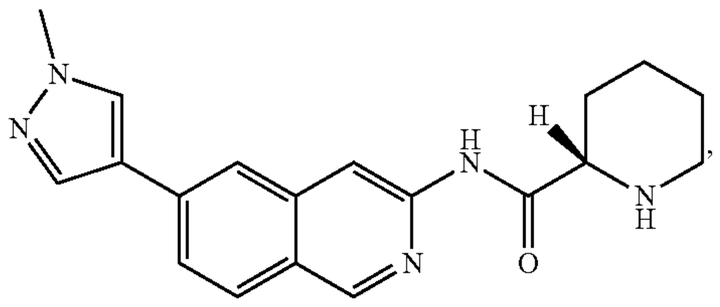

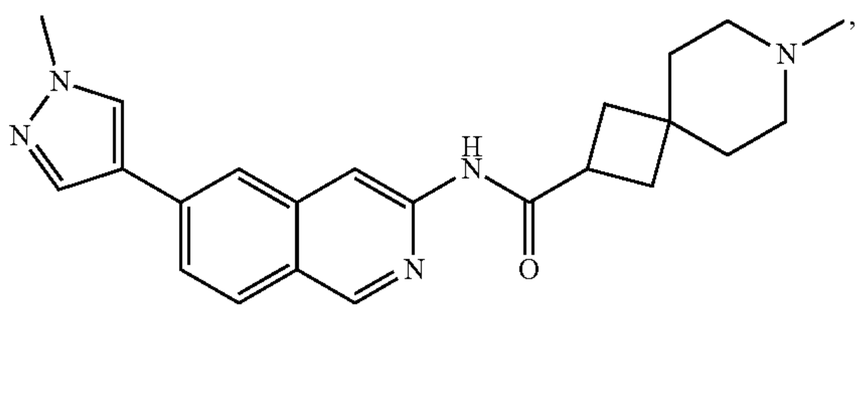

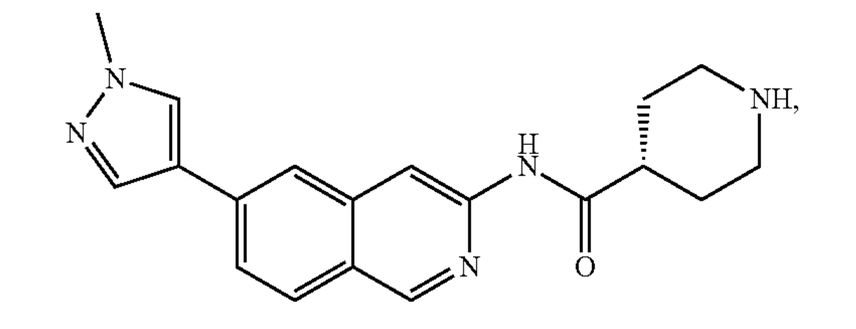

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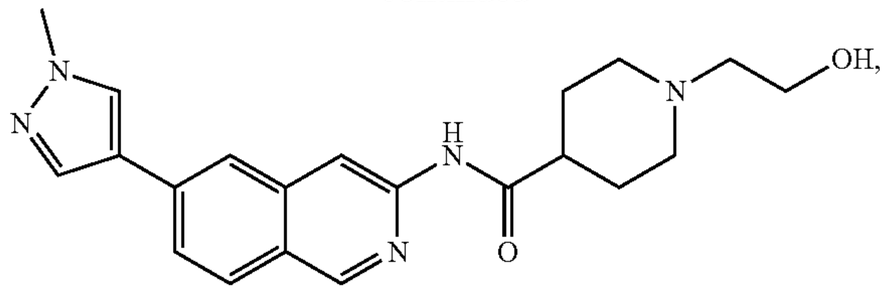

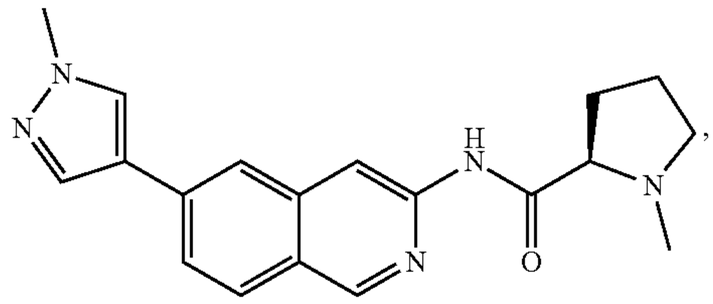

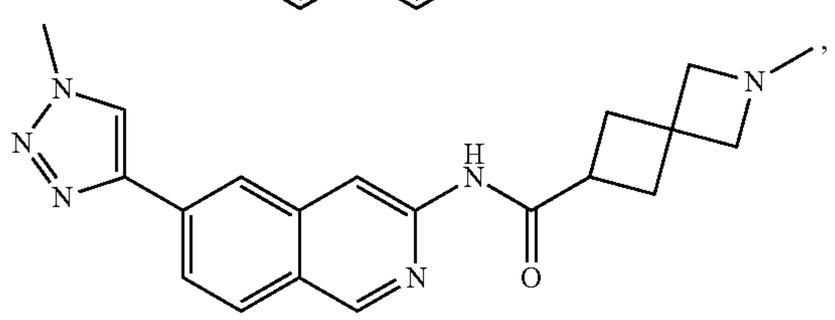

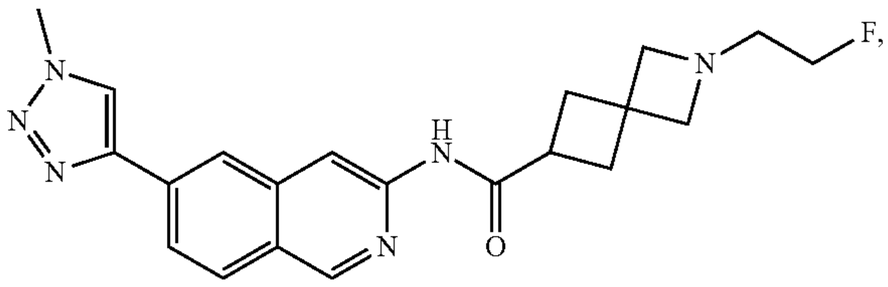

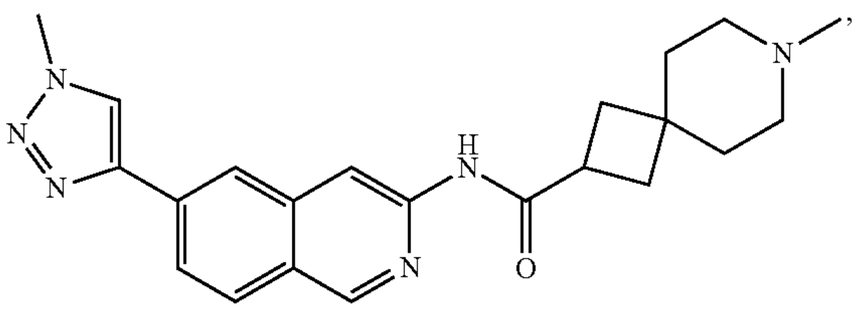

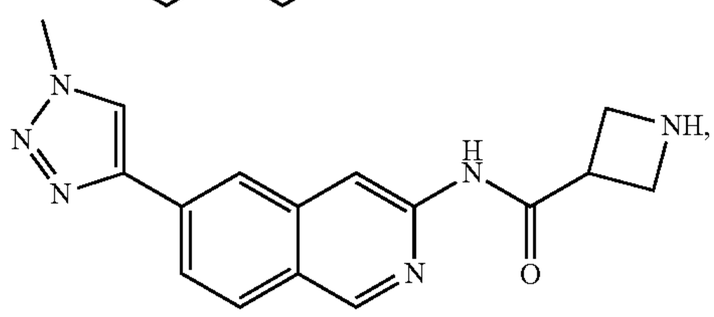

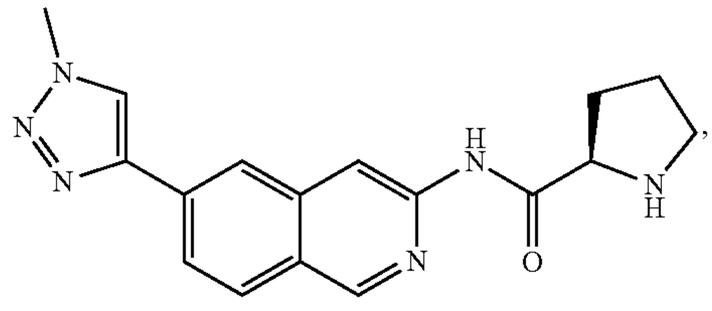

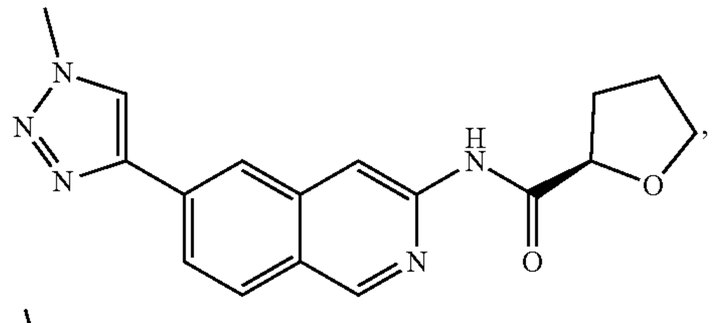

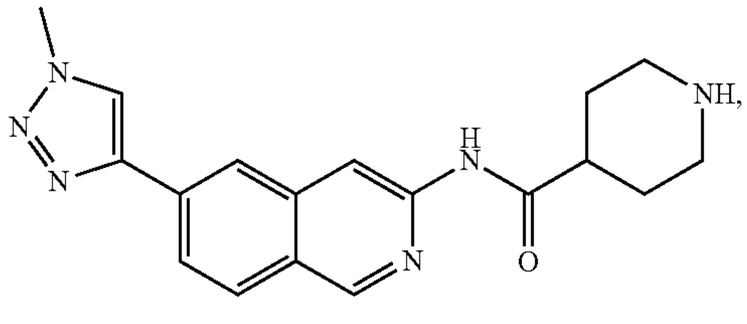

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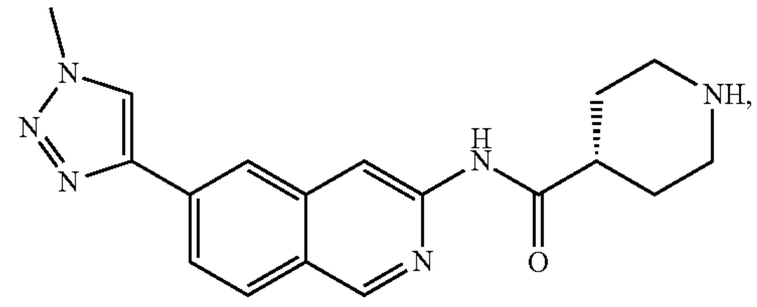

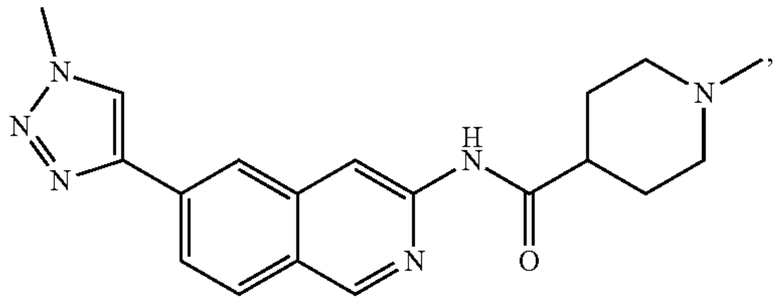

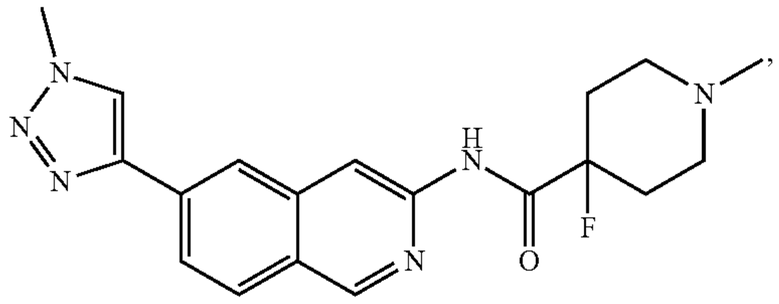

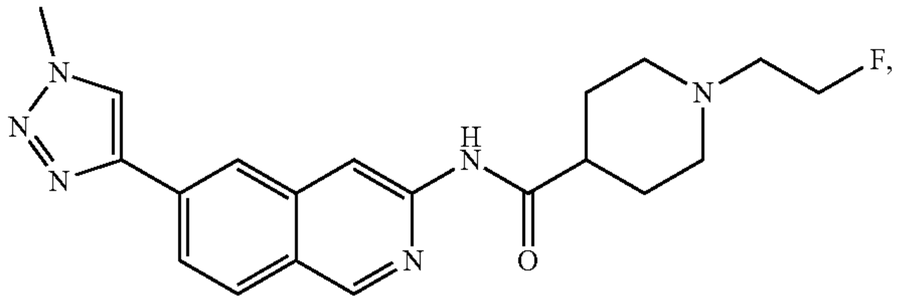

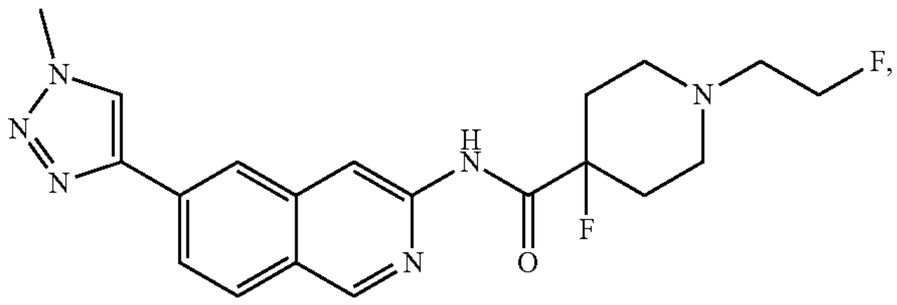

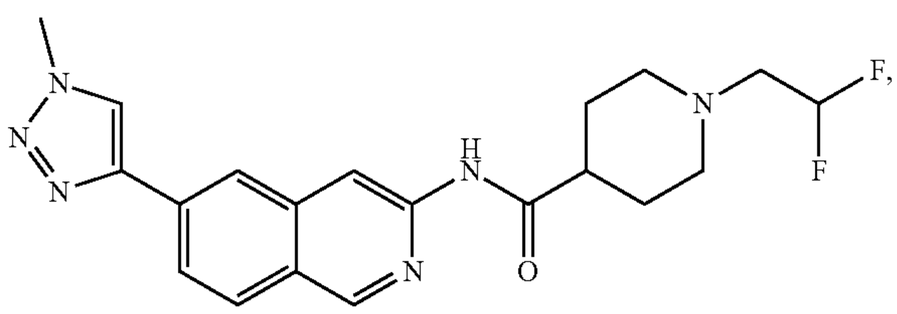

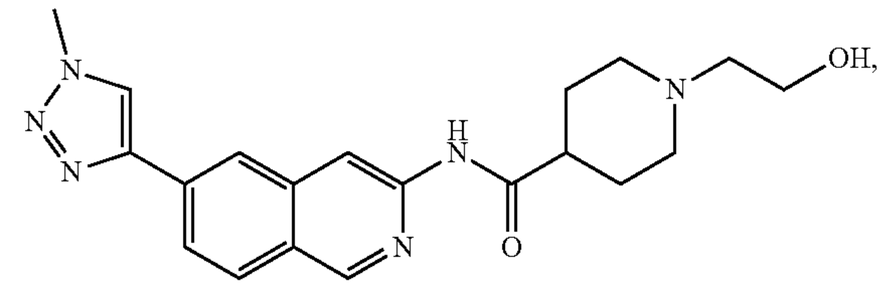

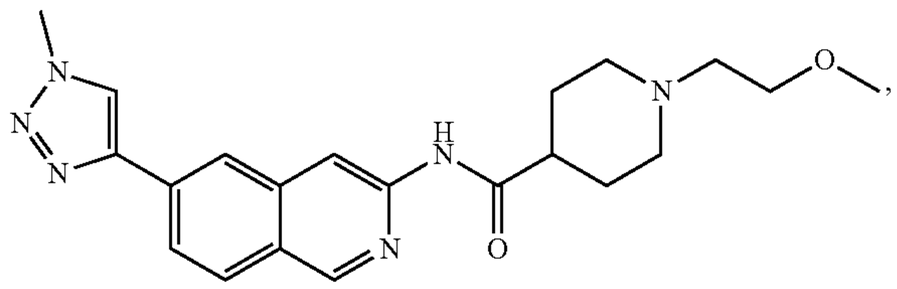

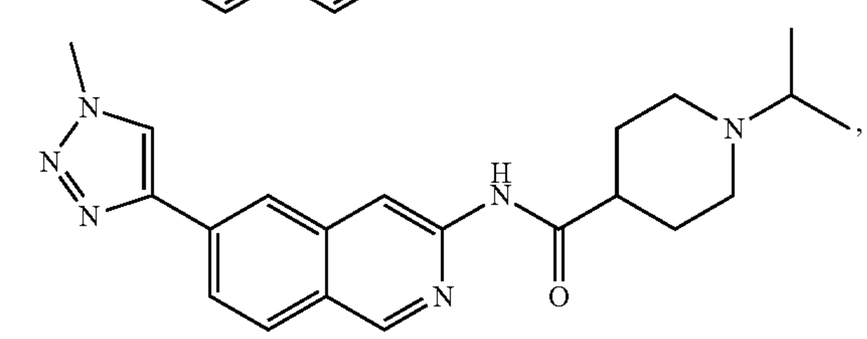

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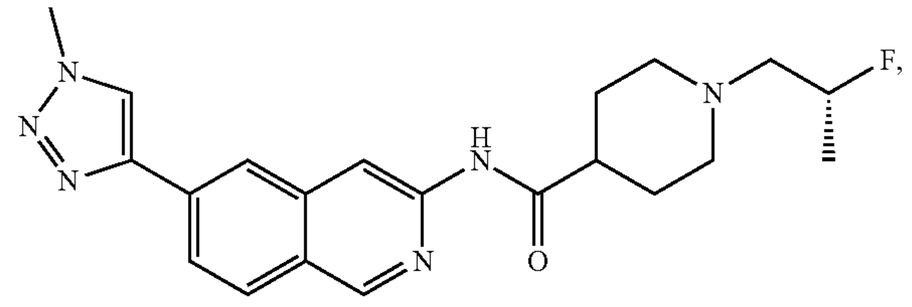

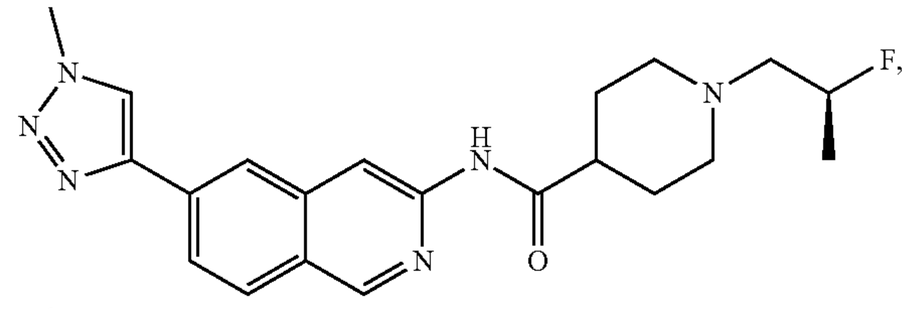

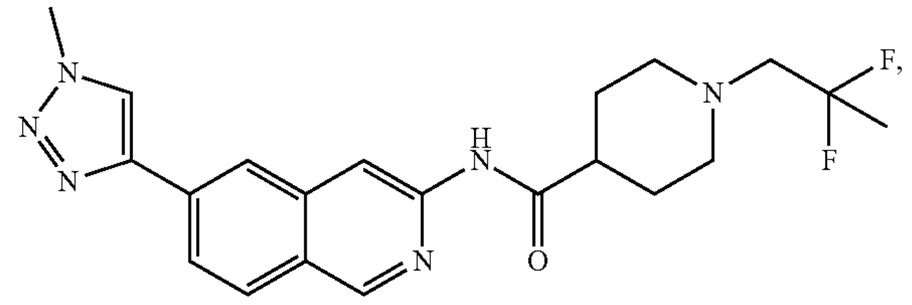

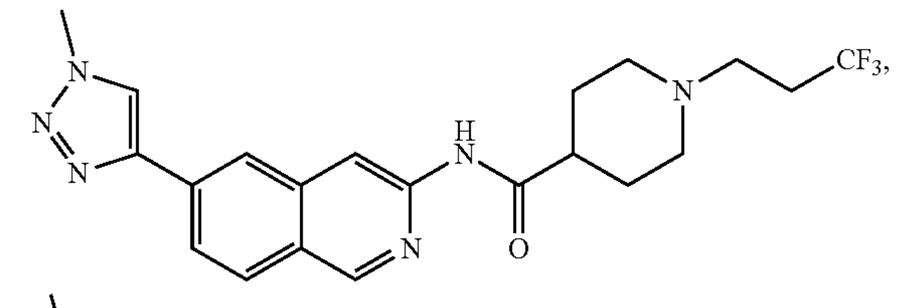

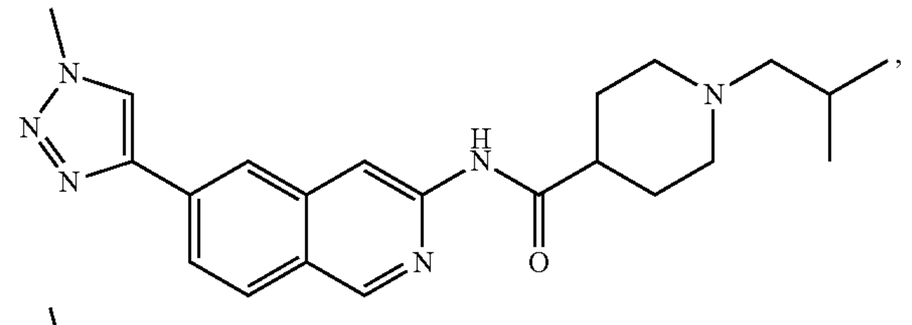

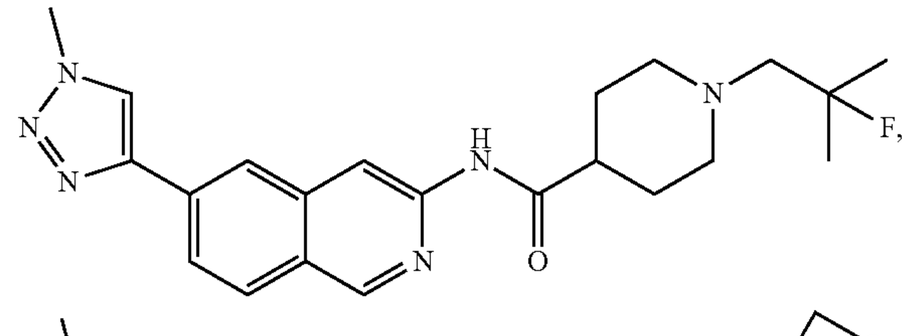

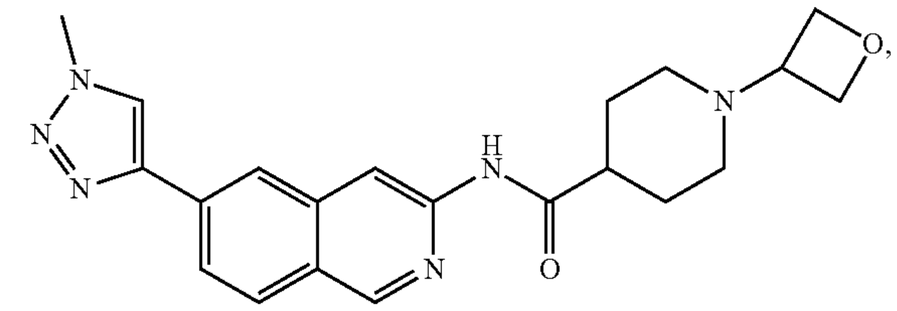

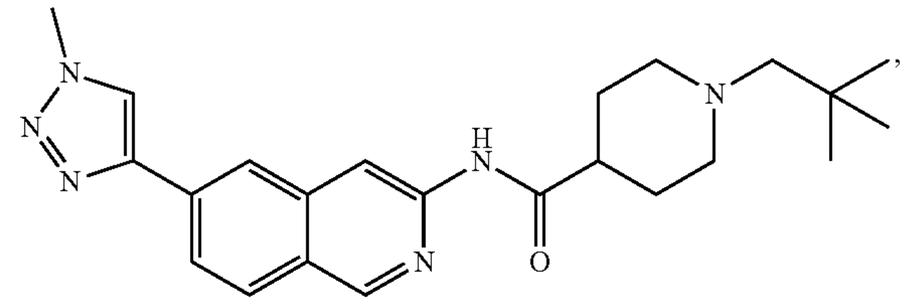

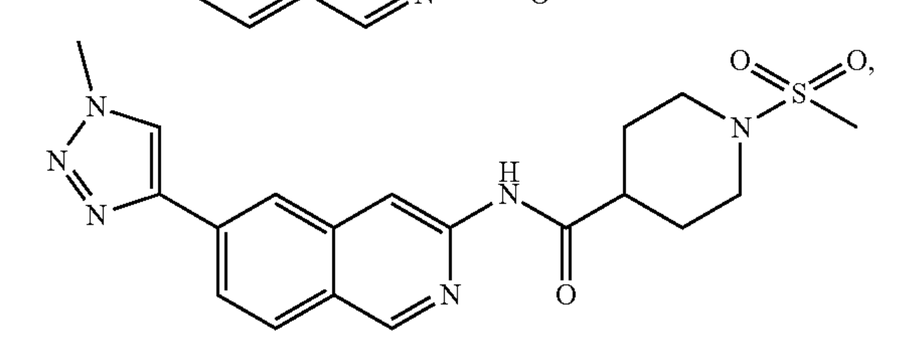

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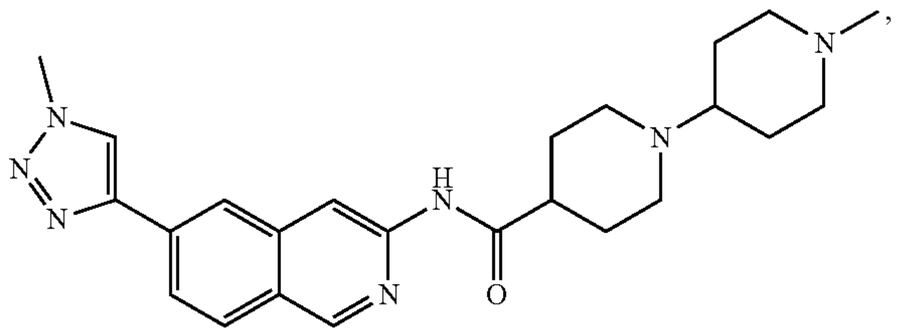

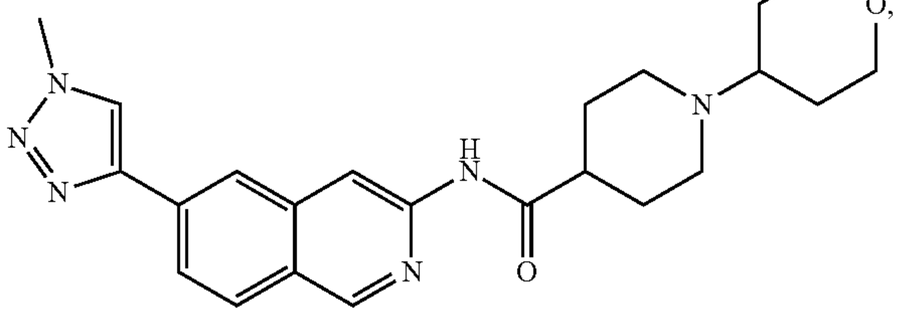

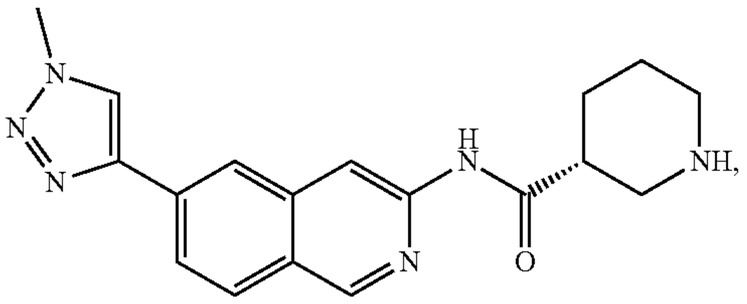

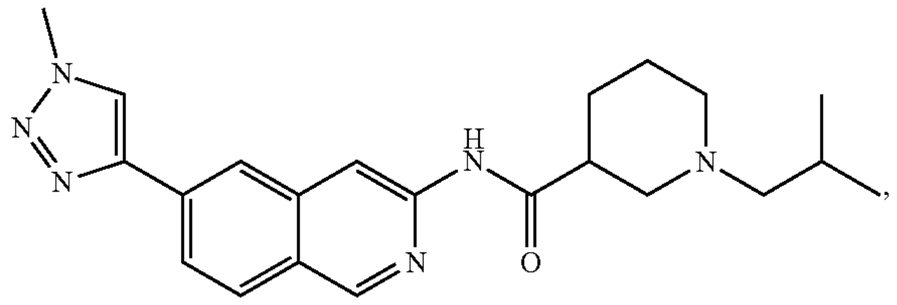

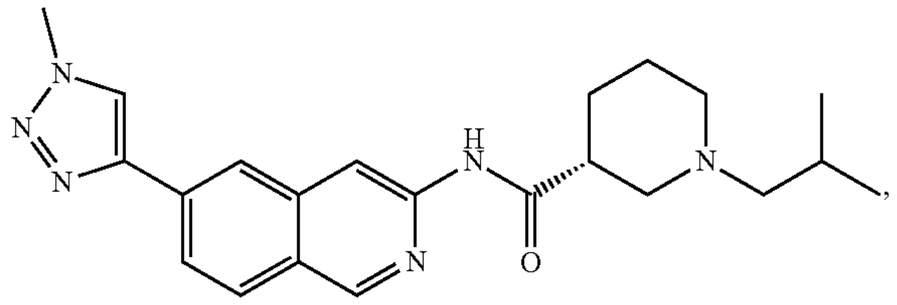

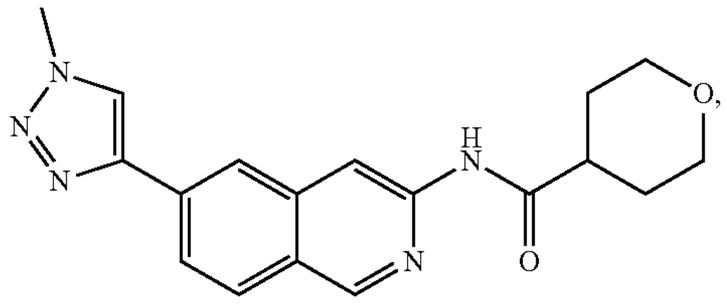

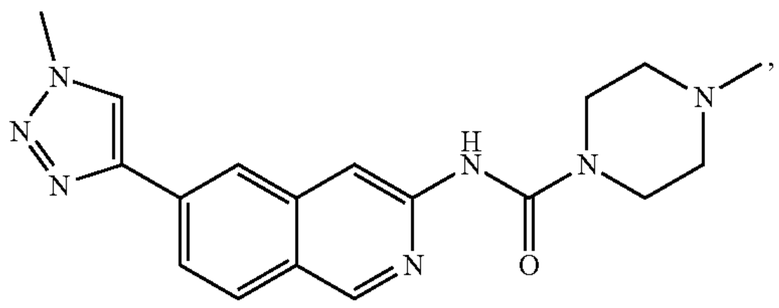

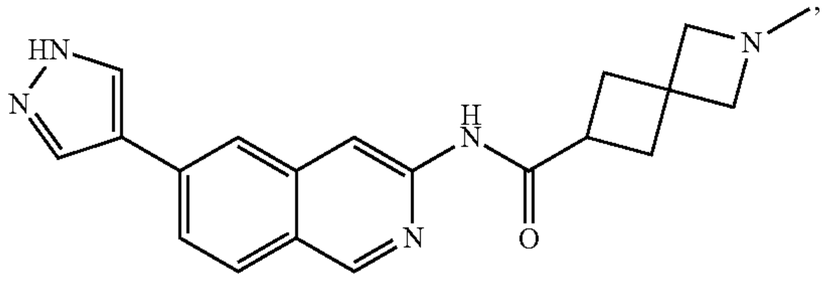

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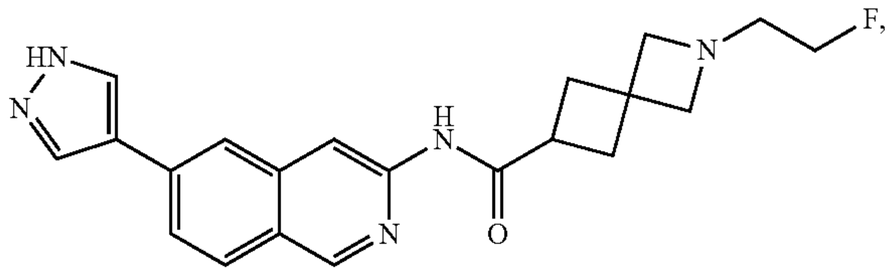

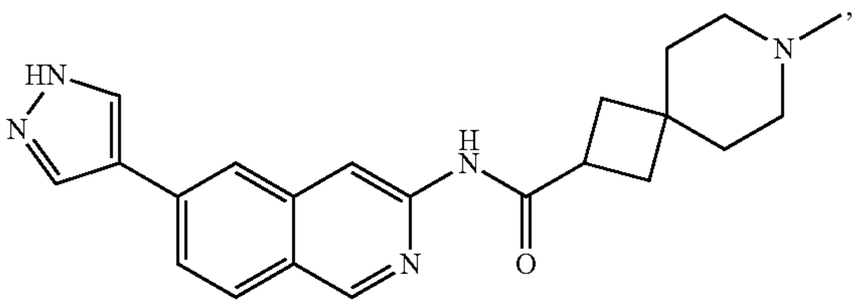

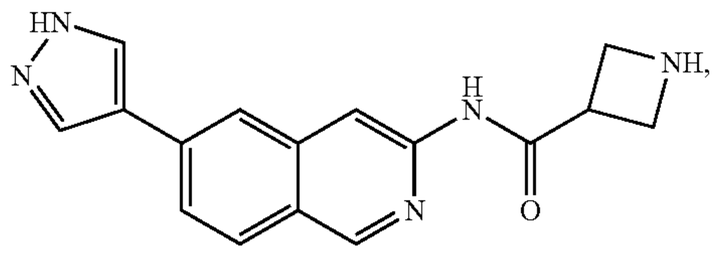

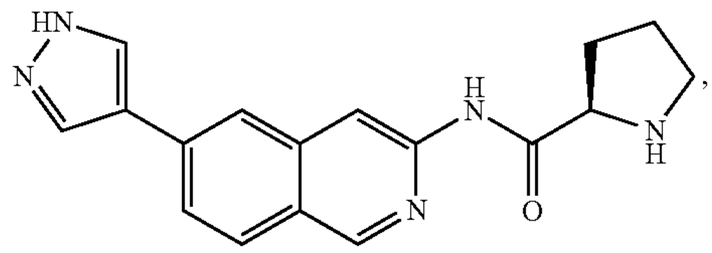

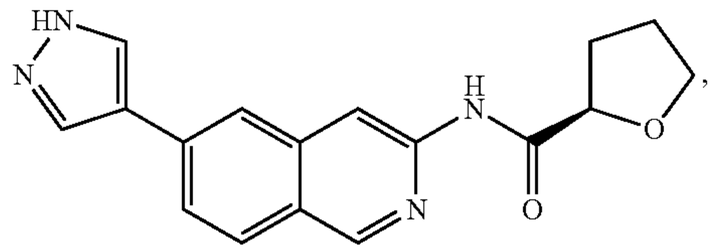

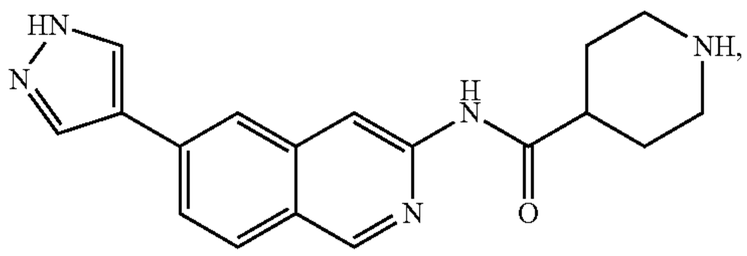

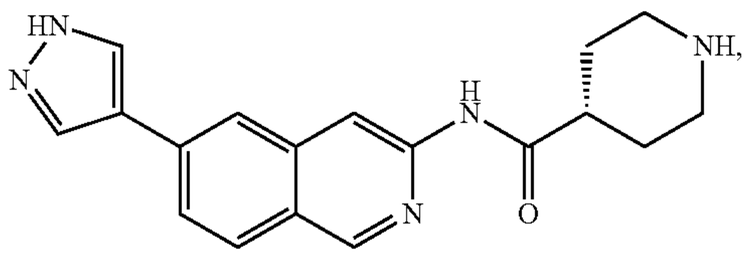

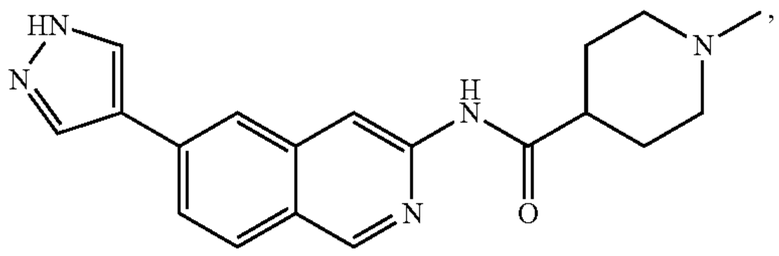

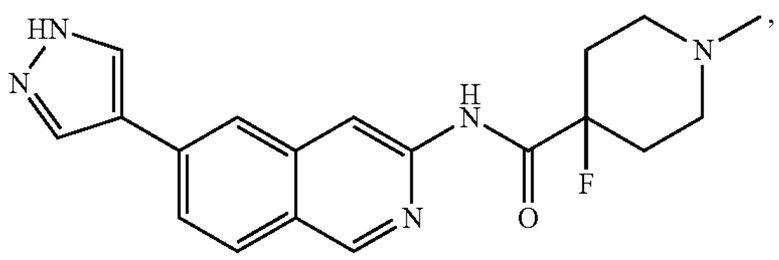

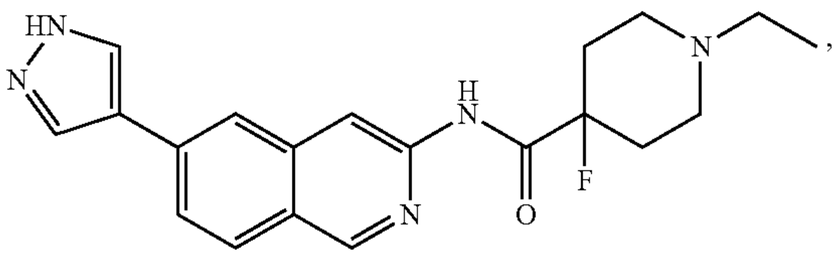

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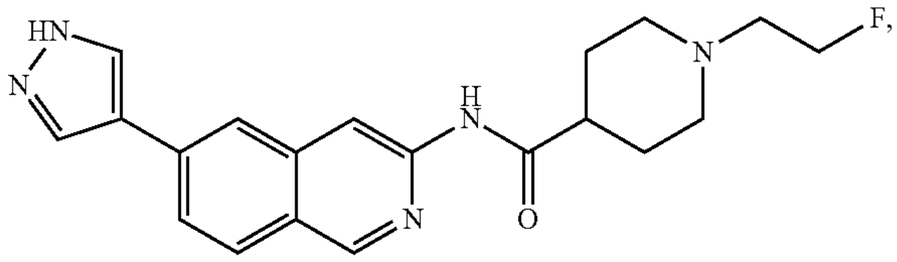

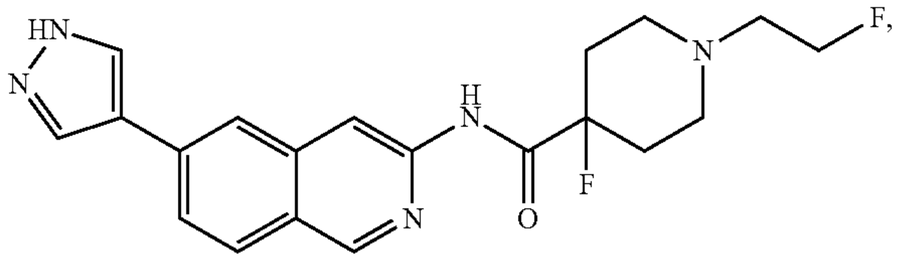

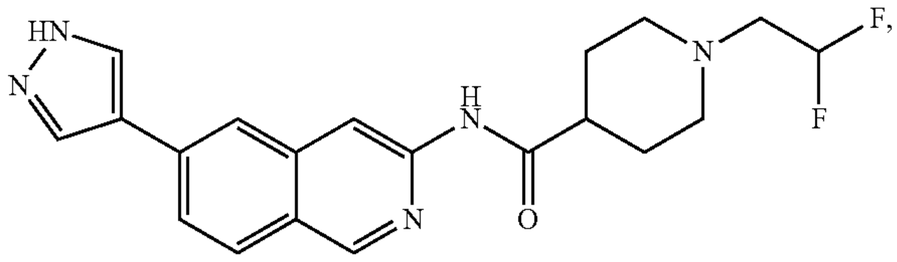

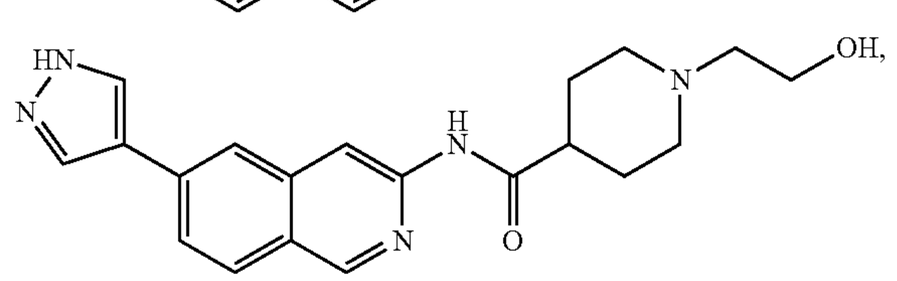

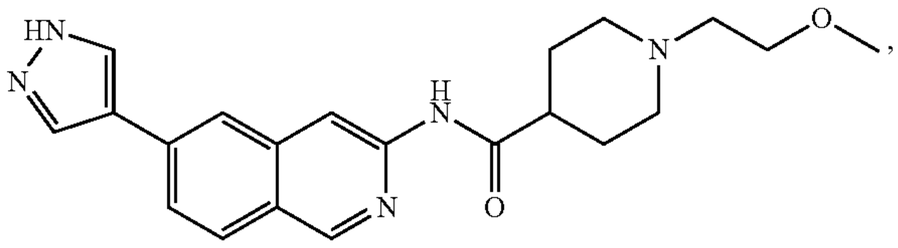

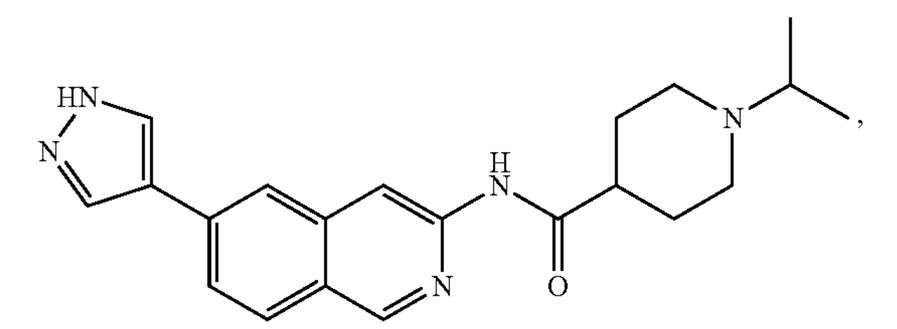

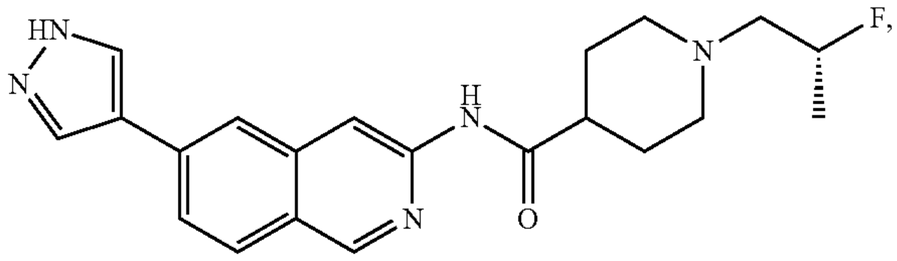

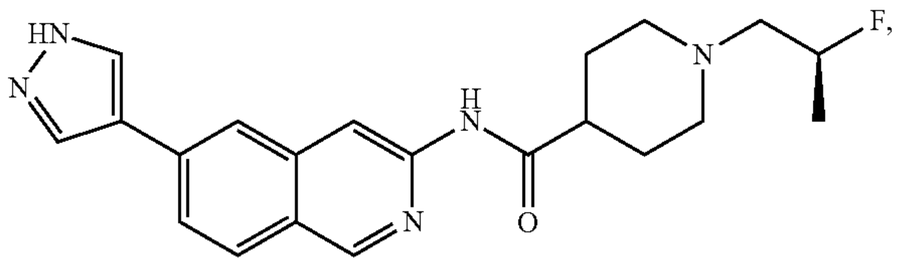

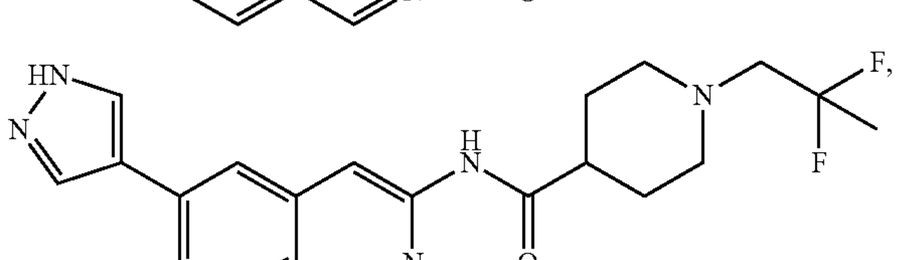

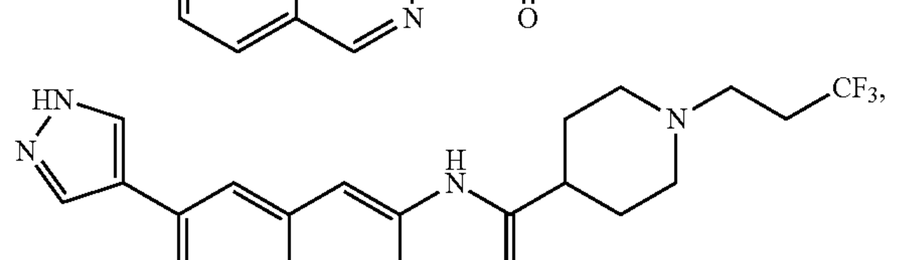

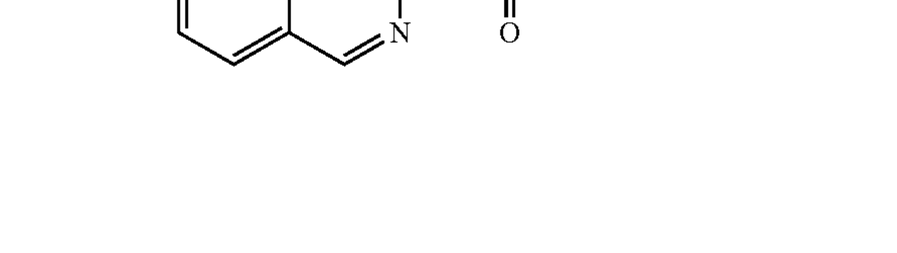

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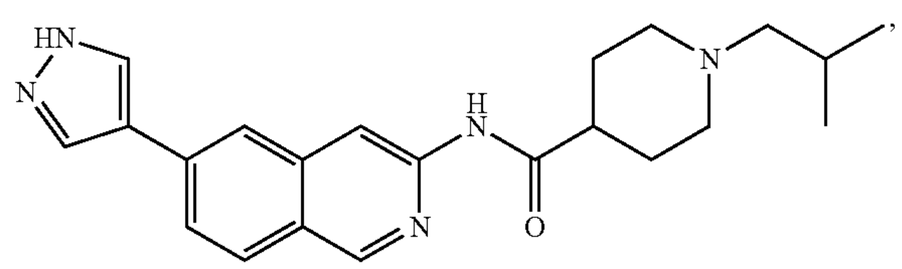

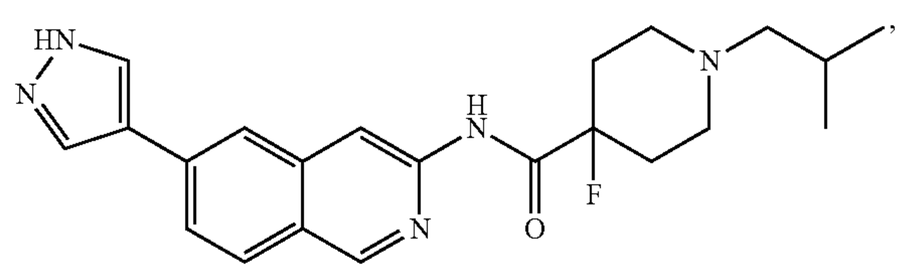

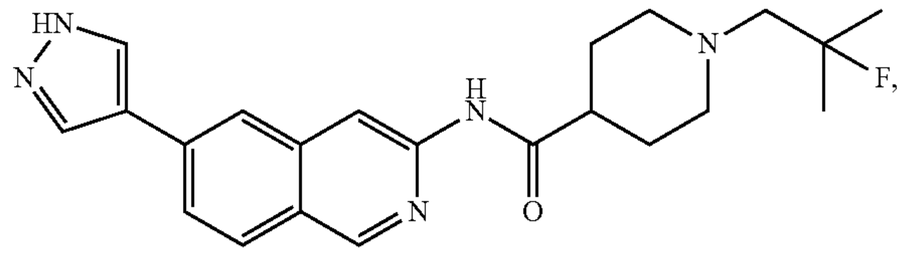

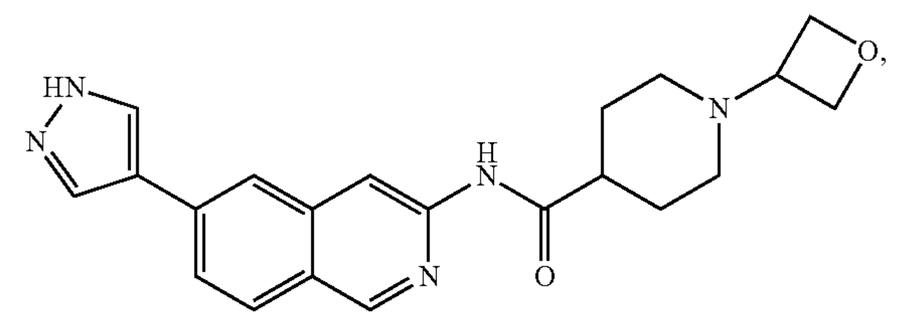

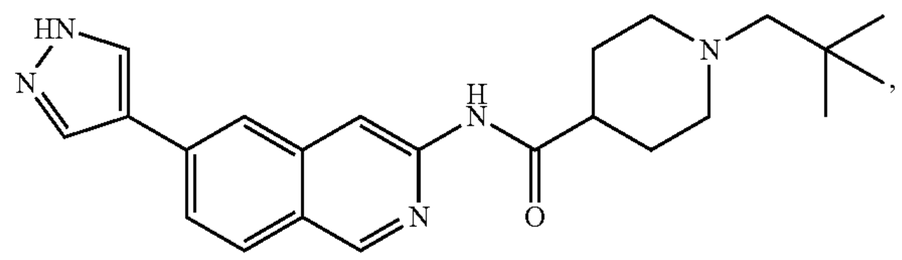

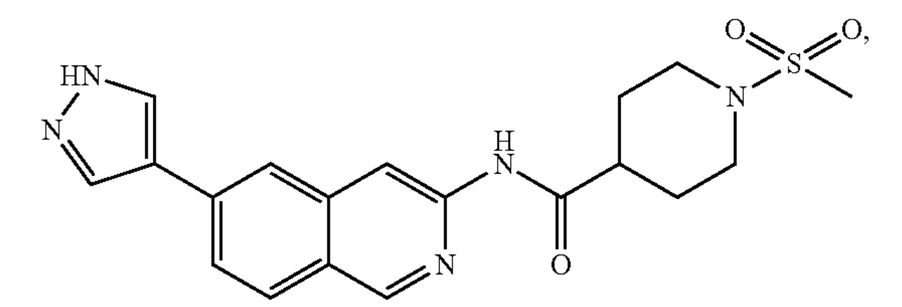

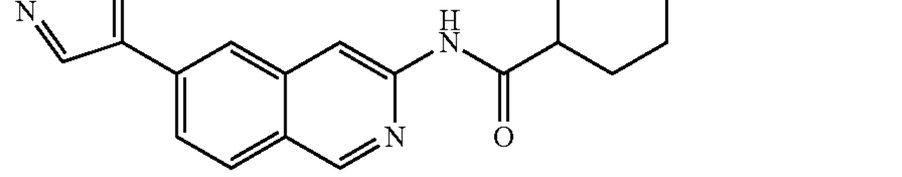

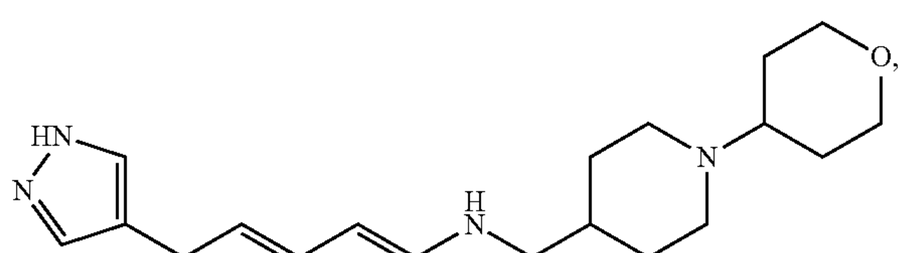

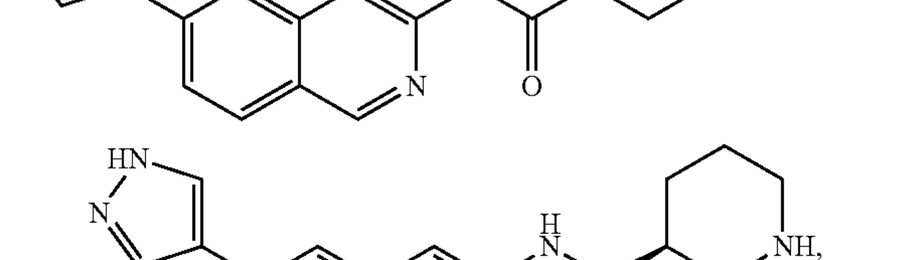

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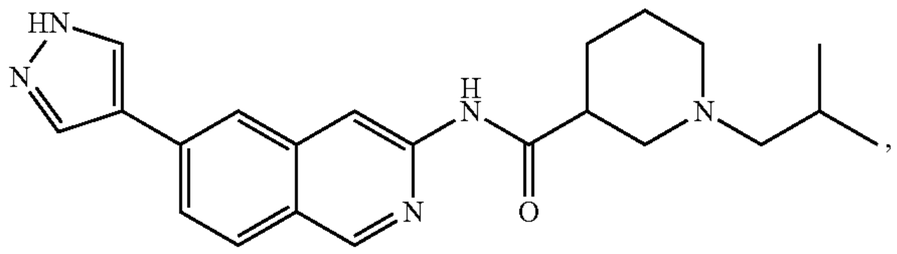

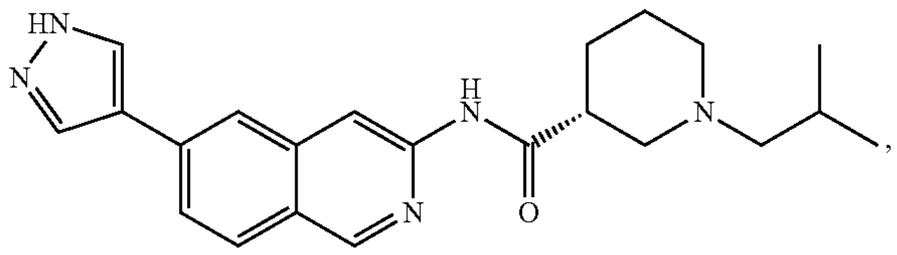

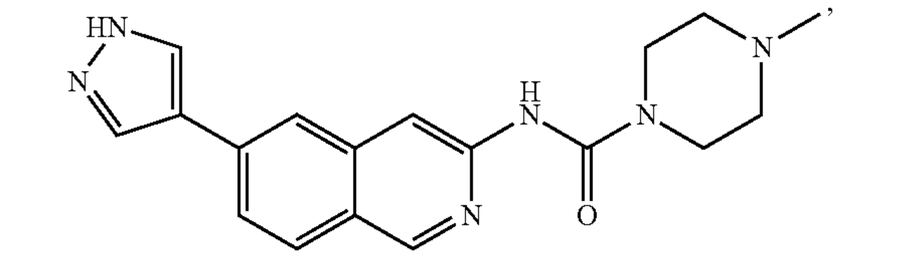

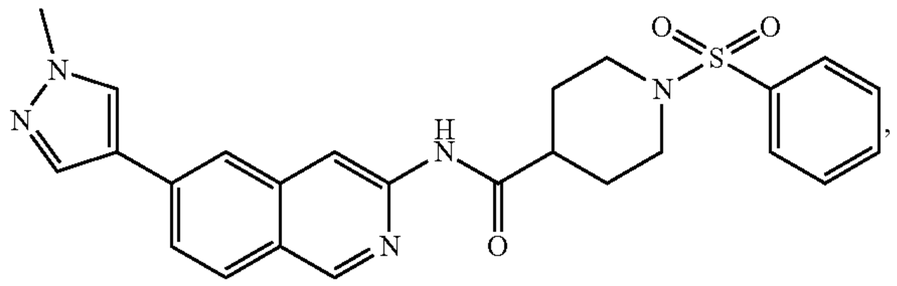

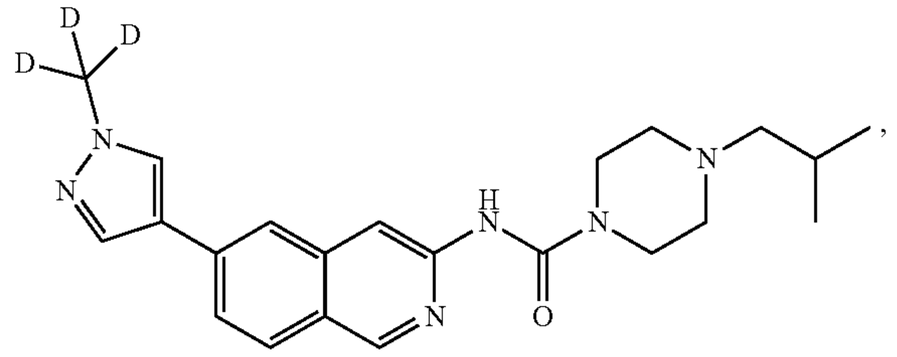

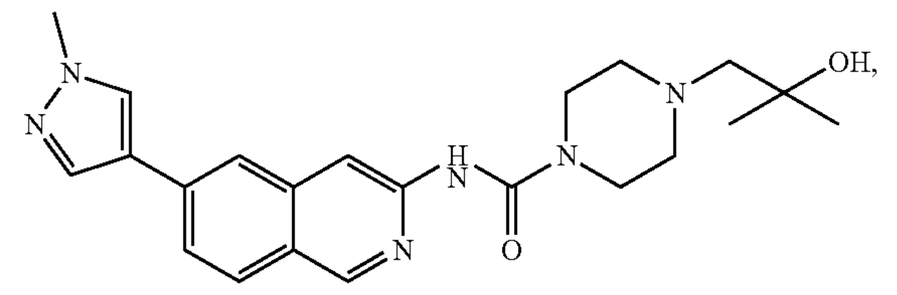

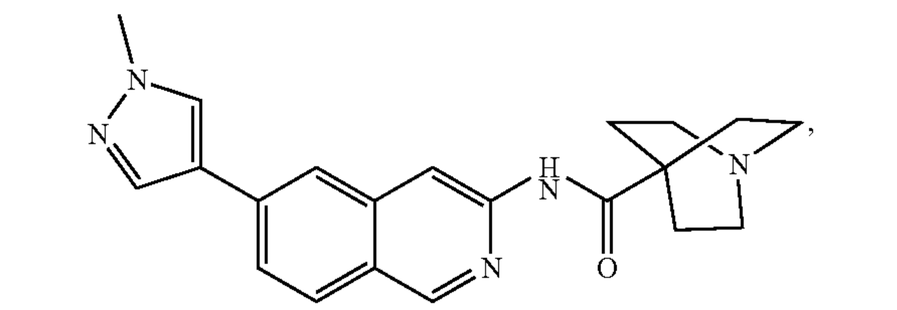

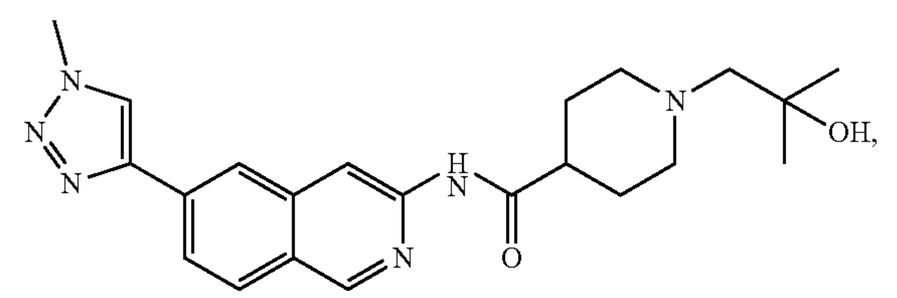

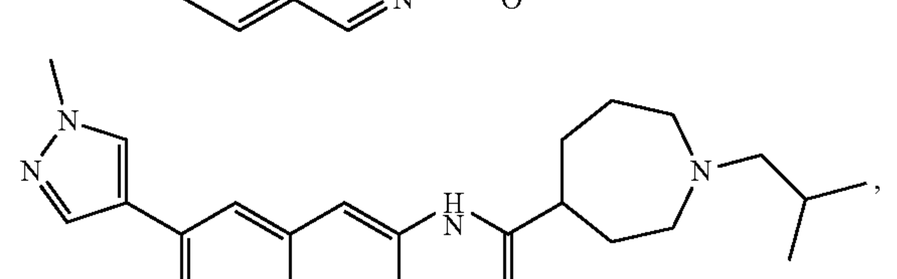

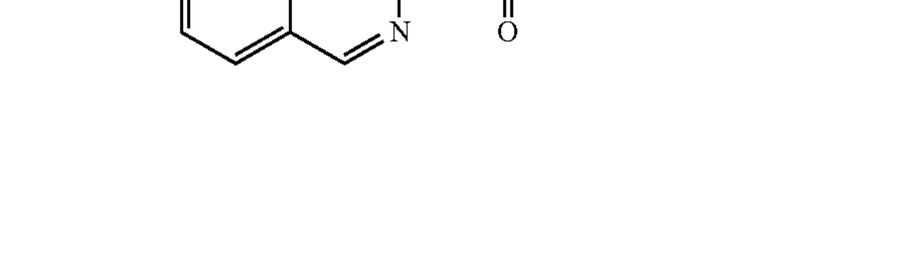

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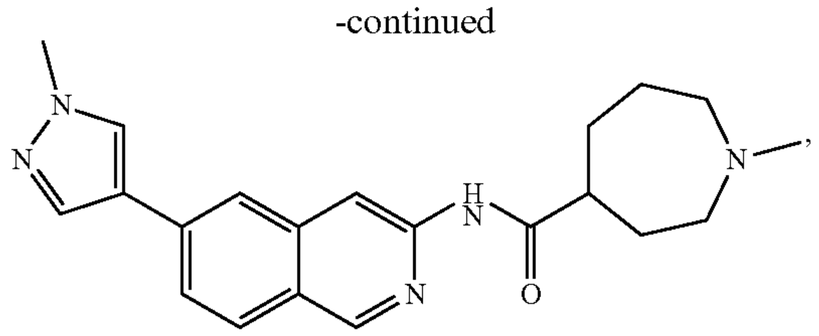
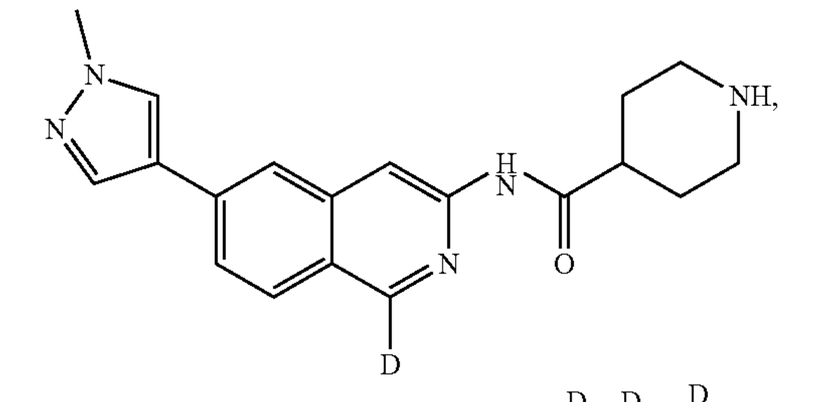
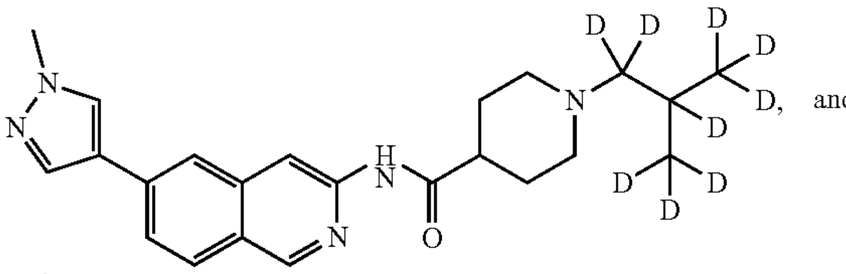
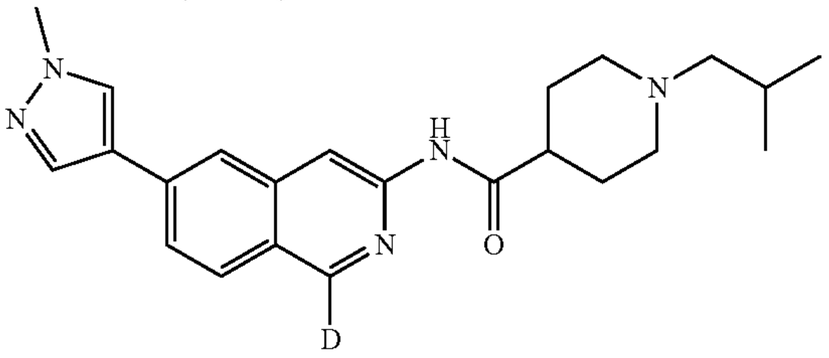


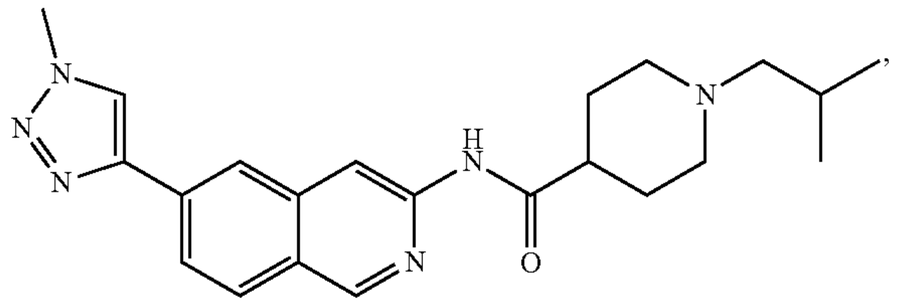


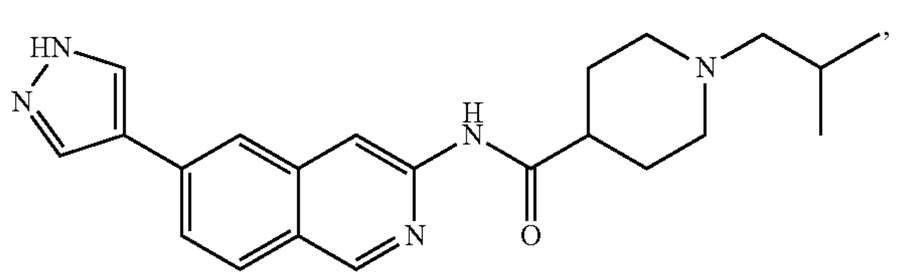


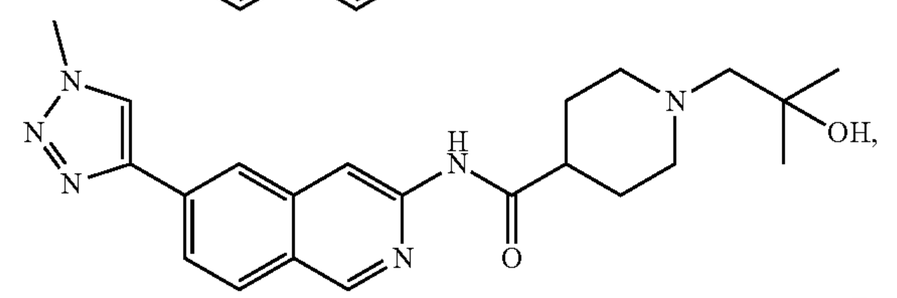


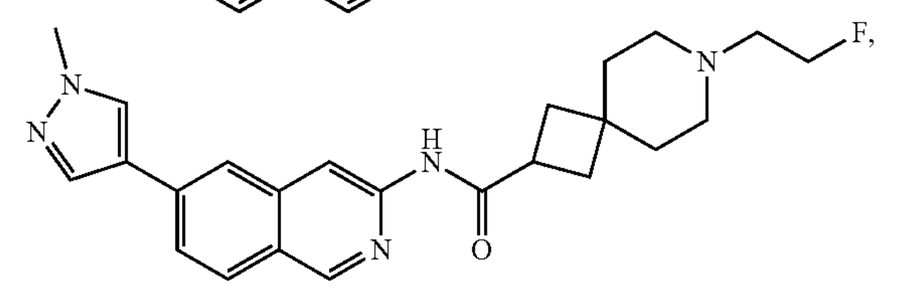
or a pharmaceutically acceptable salt thereof.

18. The compound of claim **17**, wherein the compound of Formula I is selected from the group consisting of:









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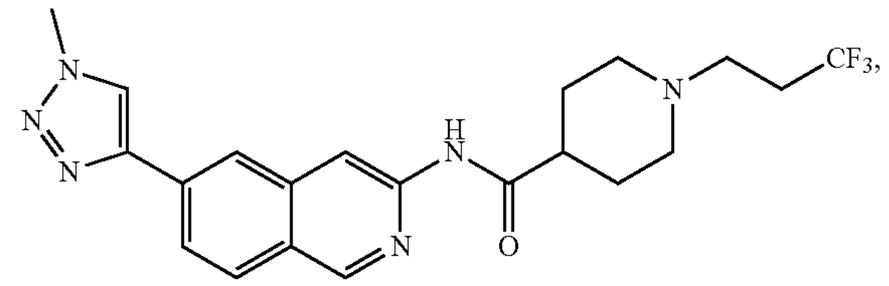

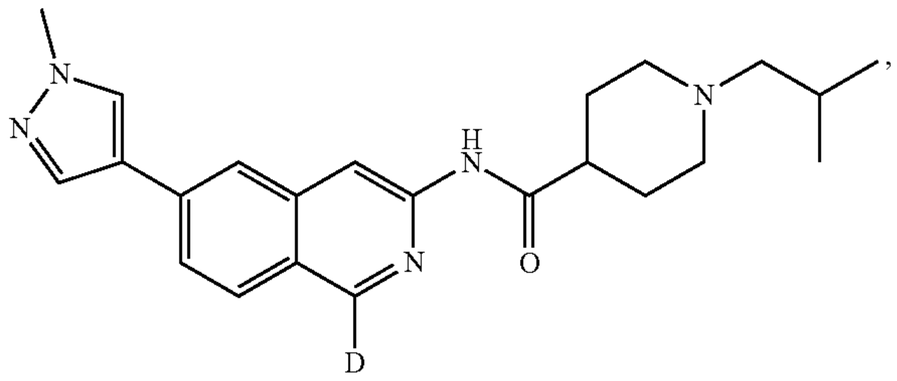

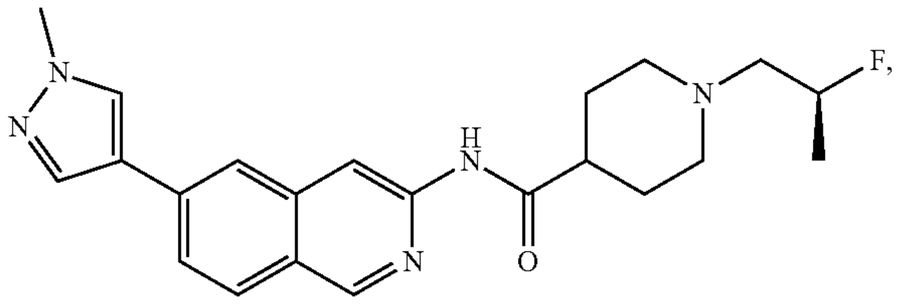

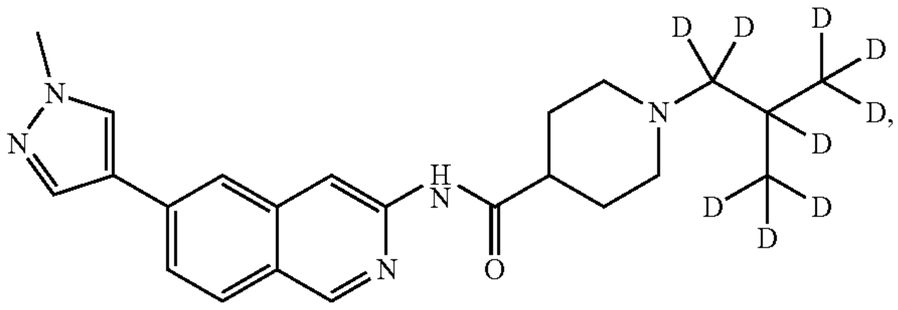

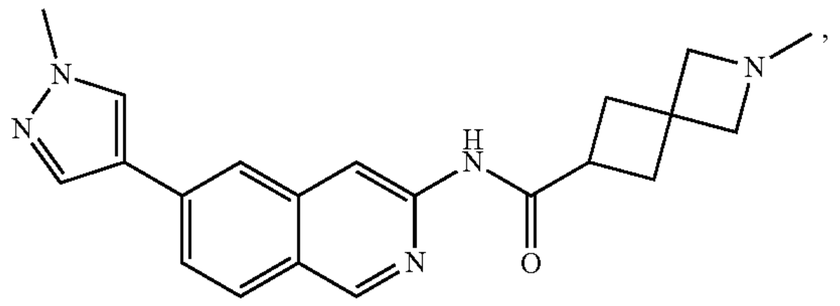

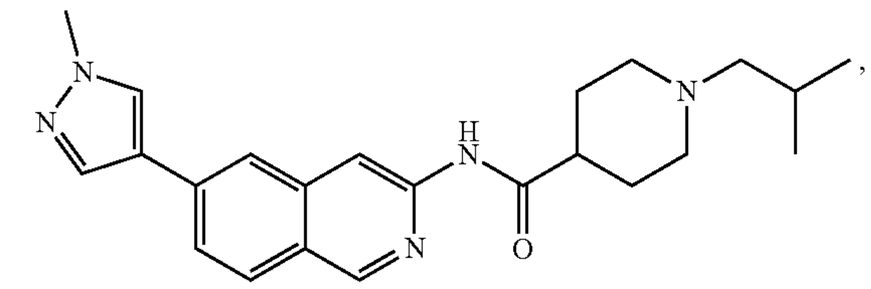

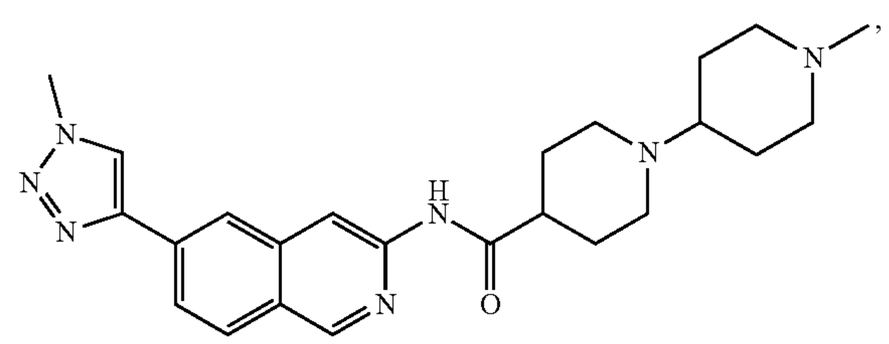

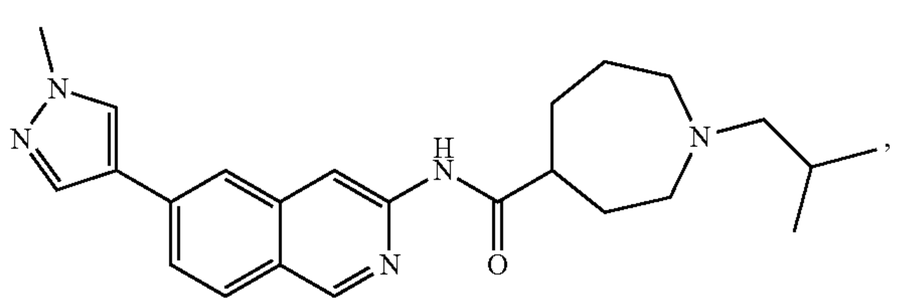

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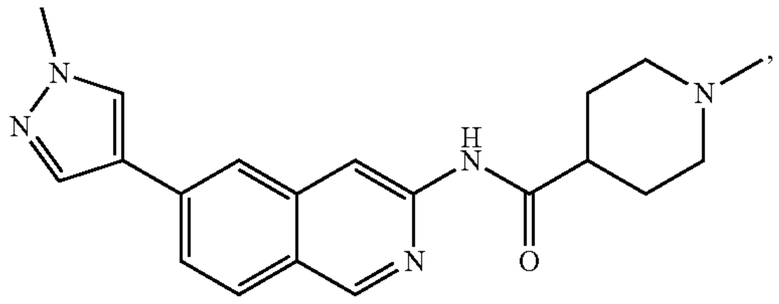
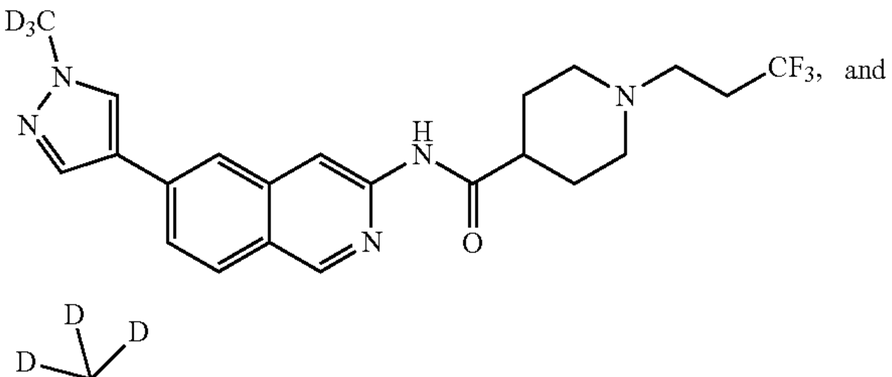
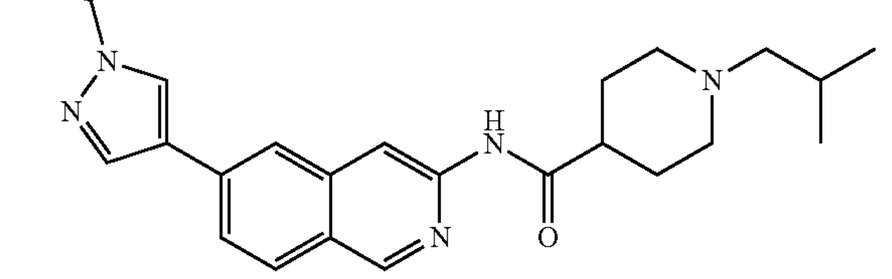
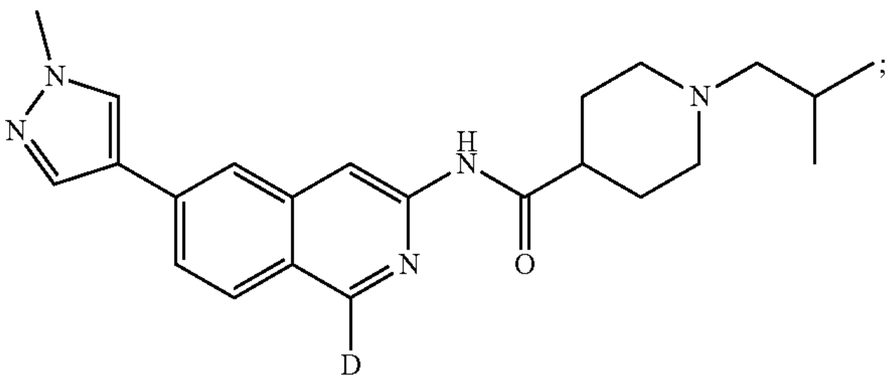






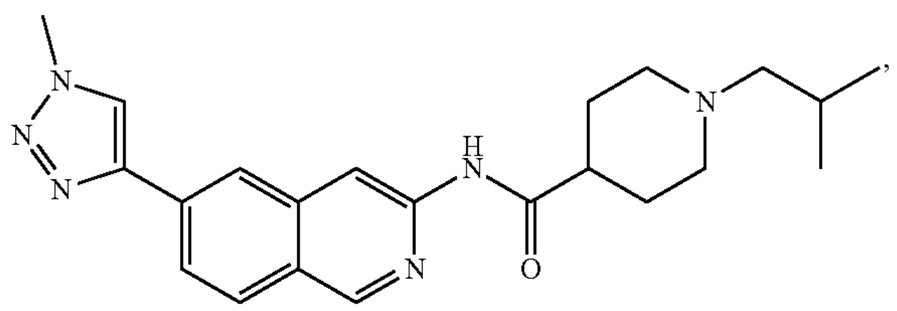


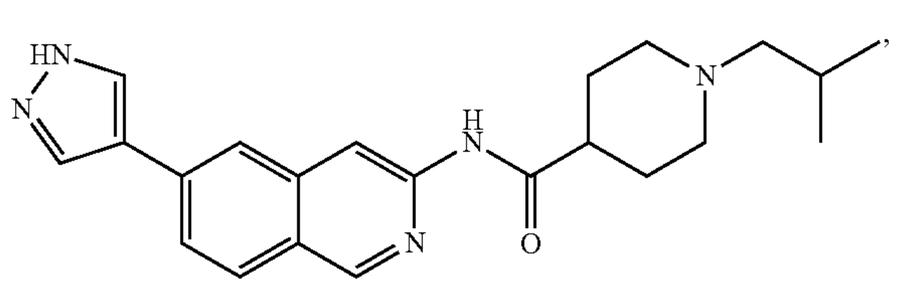
or a pharmaceutically acceptable salt thereof.

19. A pharmaceutical composition comprising a therapeutically effective amount of a compound of claim **1**, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

20. A pharmaceutical composition comprising a therapeutically effective amount of a compound of claim **17**, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

21. A pharmaceutical composition comprising a therapeutically effective amount of a compound having a structure selected from the group consisting of:





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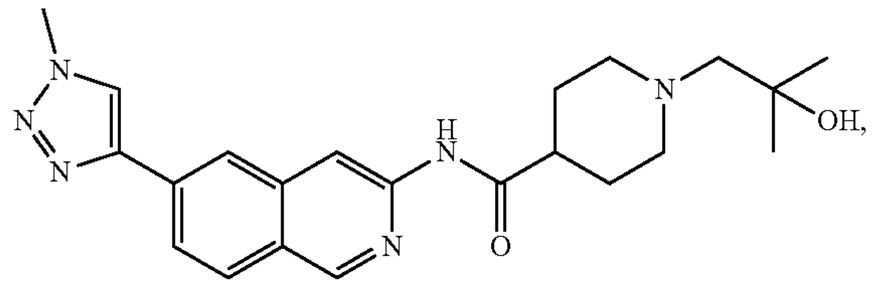

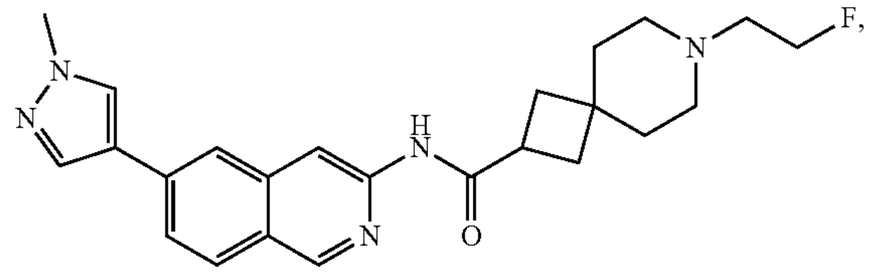

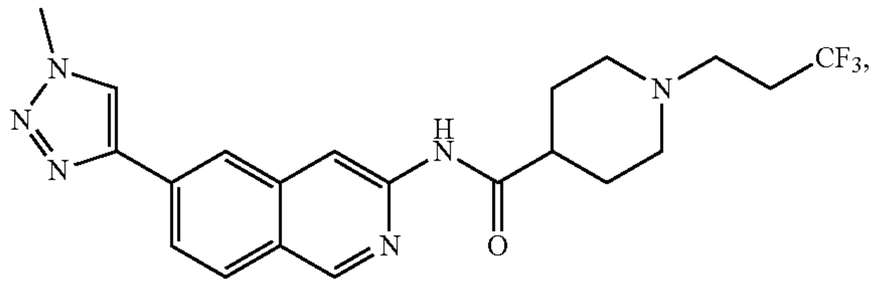

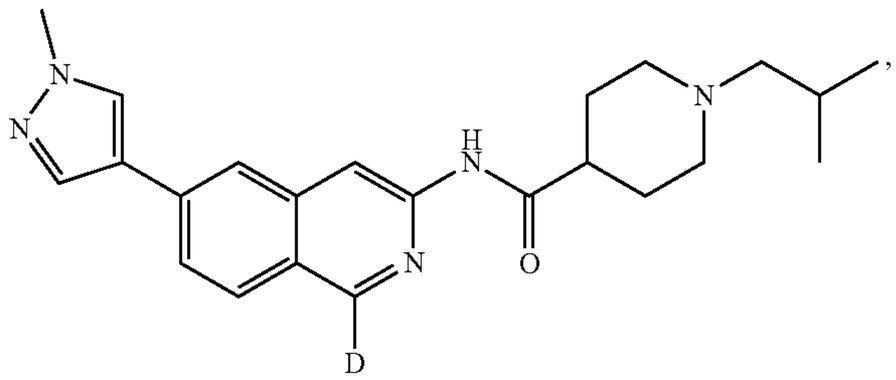

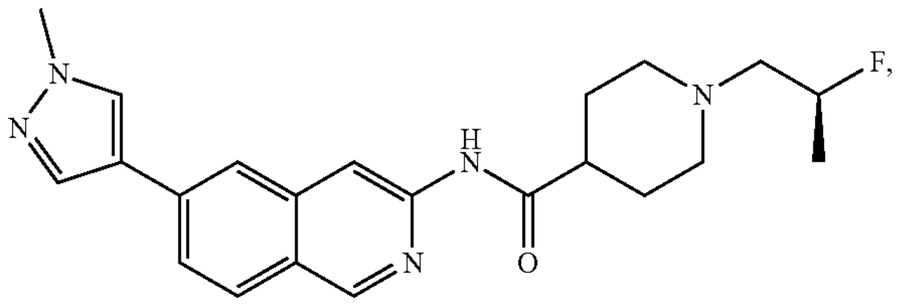

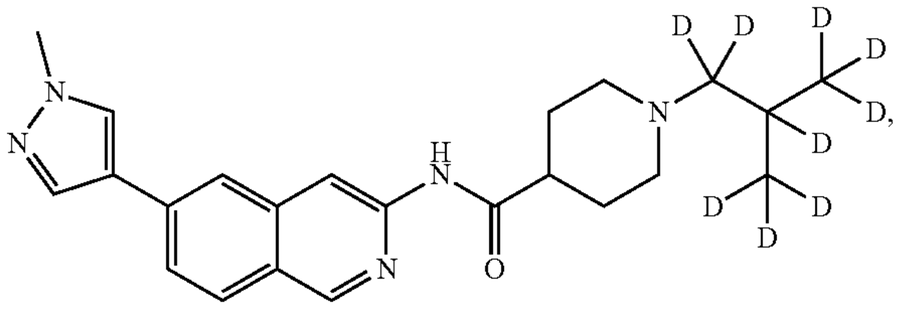

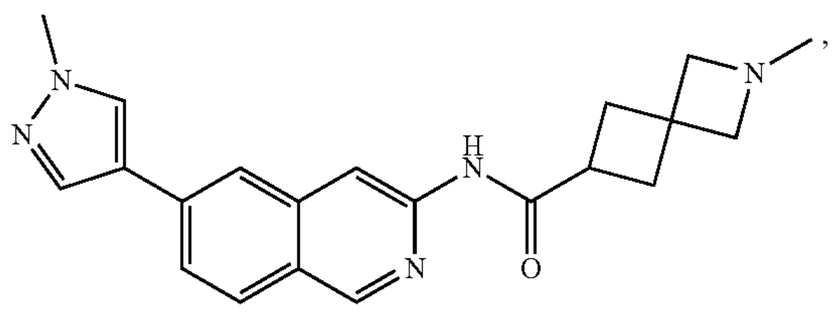

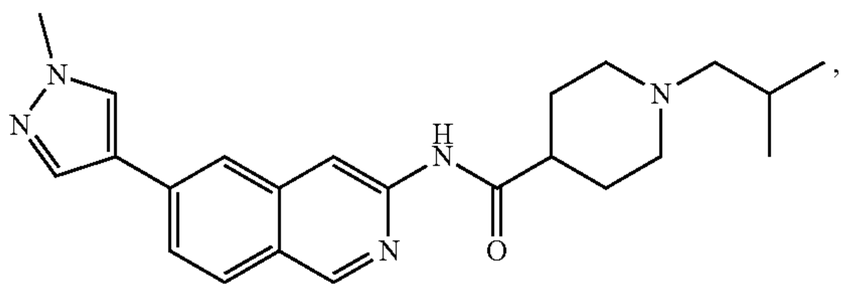

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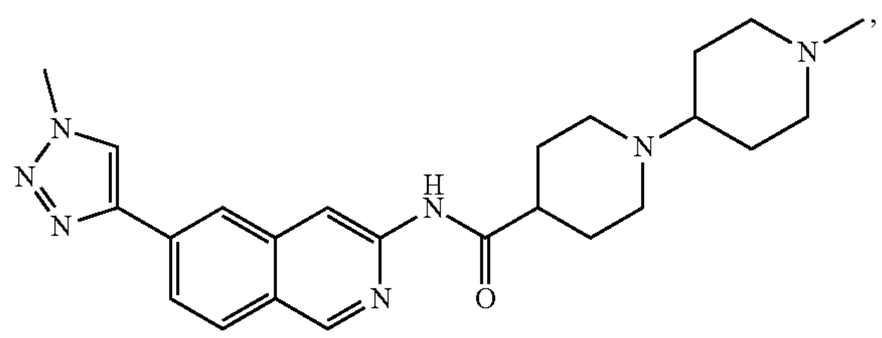
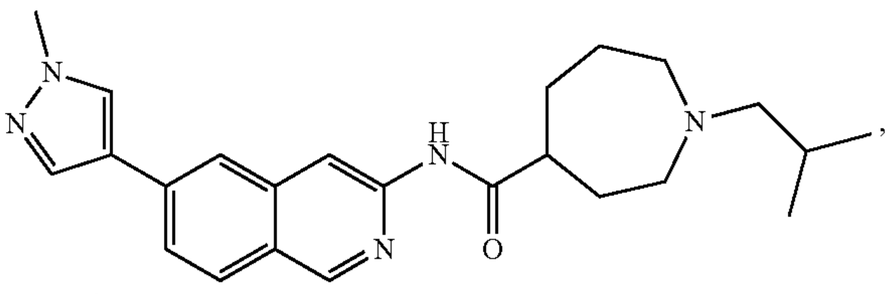
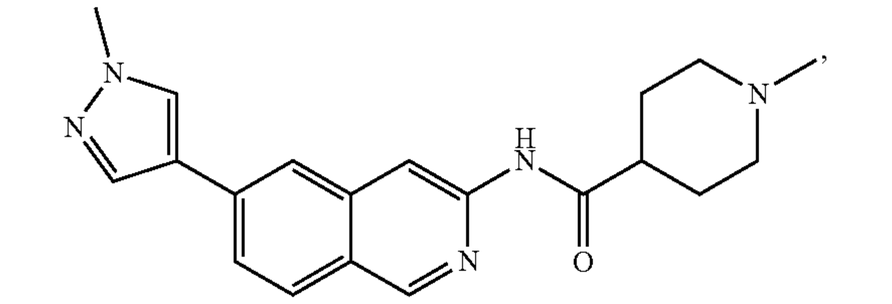
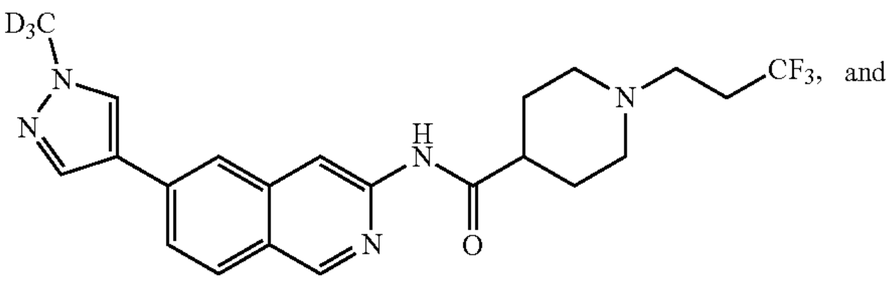
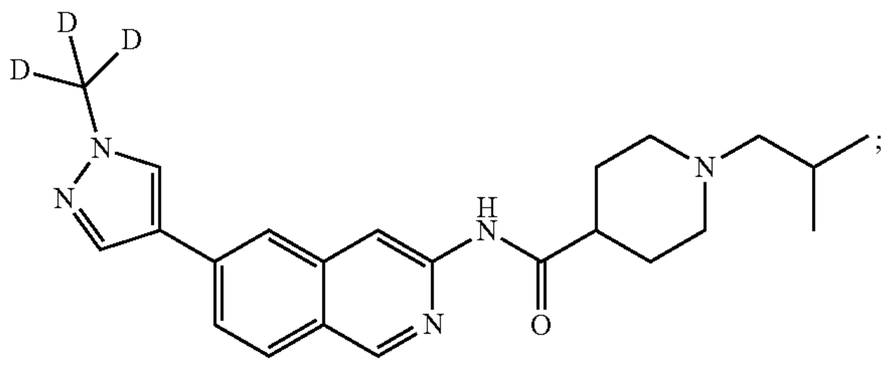




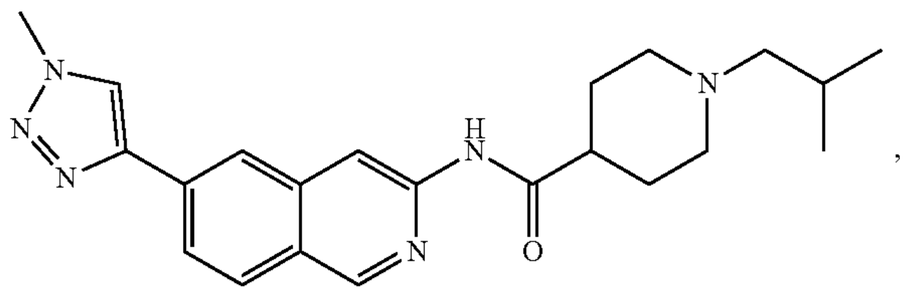






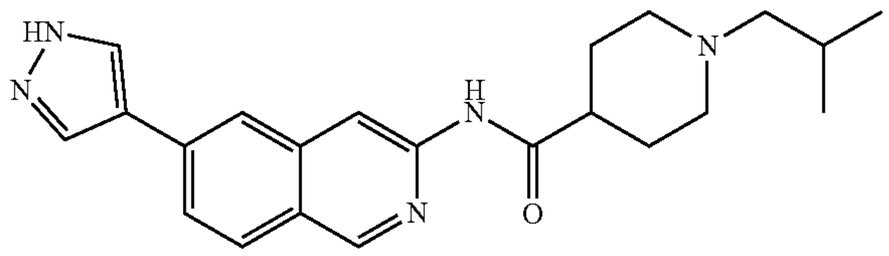
or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

22. The compound of claim **17**, wherein the compound of Formula I is:



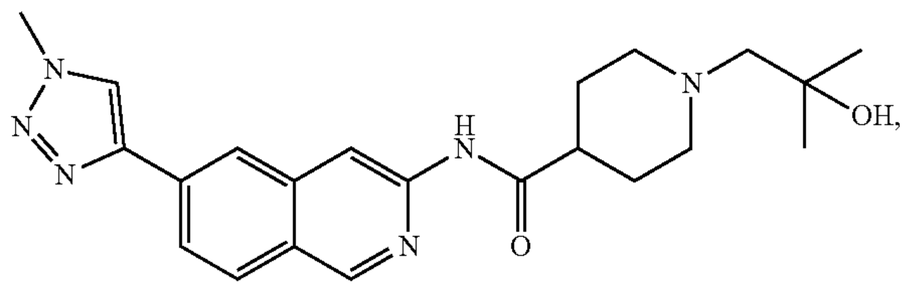
or a pharmaceutically acceptable salt thereof.

23. The compound of claim **17**, wherein the compound of Formula I is:



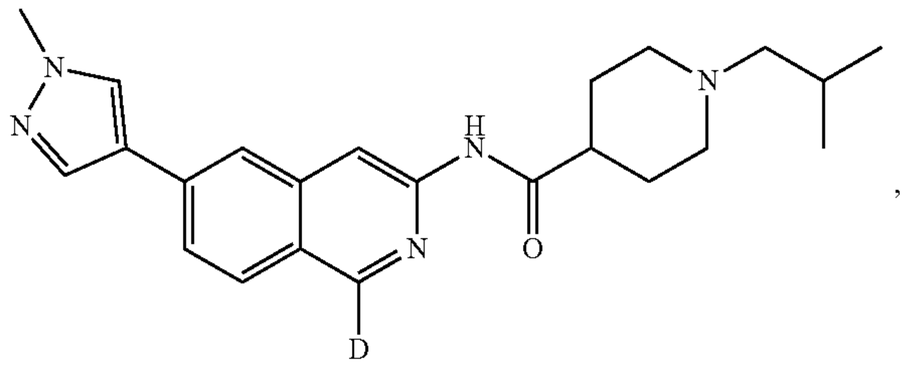
or a pharmaceutically acceptable salt thereof.

24. The compound of claim **17**, wherein the compound of Formula I is:



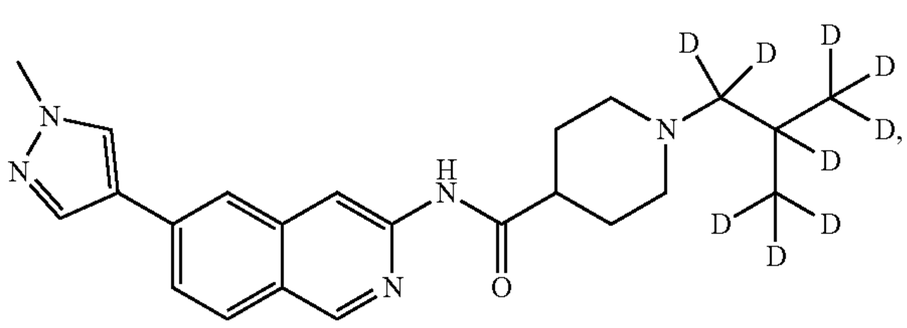
or a pharmaceutically acceptable salt thereof.

25. The compound of claim **17**, wherein the compound of Formula I is:



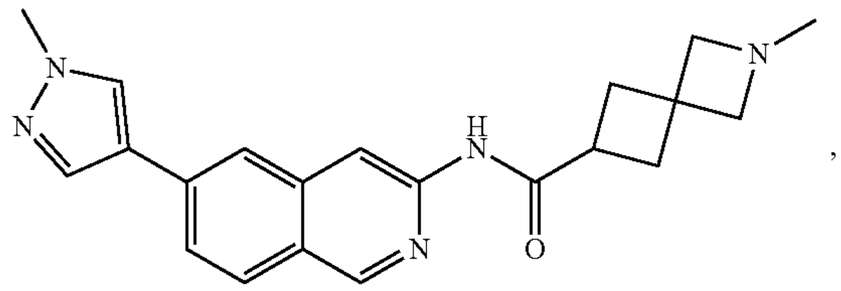
or a pharmaceutically acceptable salt thereof.

26. The compound of claim **17**, wherein the compound of Formula I is:



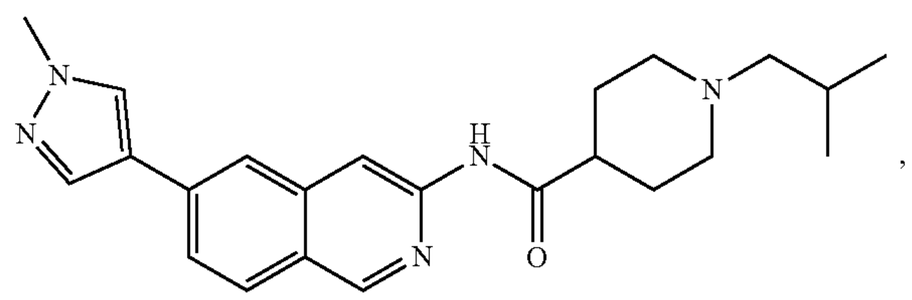
or a pharmaceutically acceptable salt thereof.

27. The compound of claim **17**, wherein the compound of Formula I is:



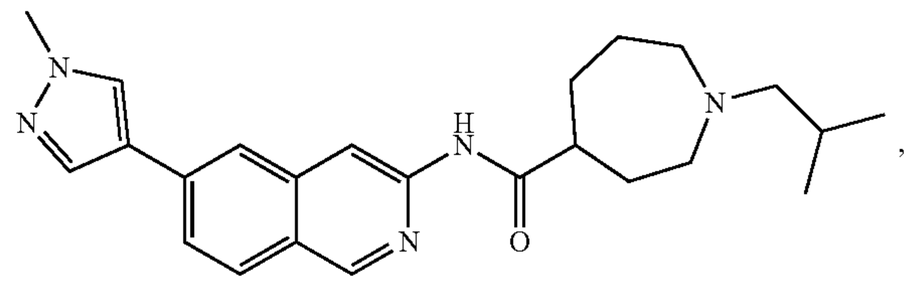
or a pharmaceutically acceptable salt thereof.

28. The compound of claim **17**, wherein the compound of Formula I is:



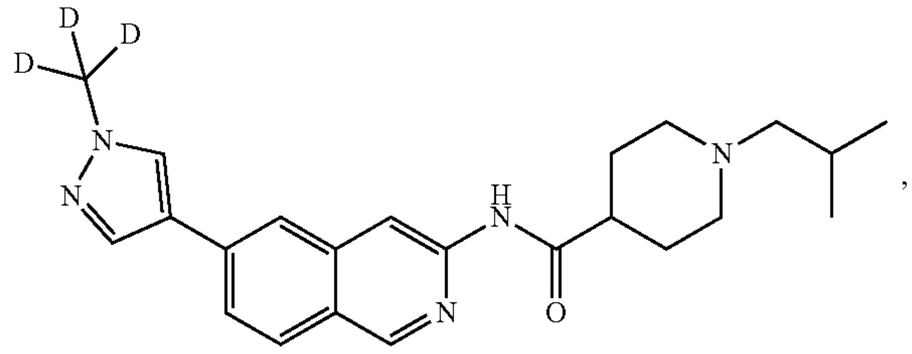
or a pharmaceutically acceptable salt thereof.

29. The compound of claim **17**, wherein the compound of Formula I is:



or a pharmaceutically acceptable salt thereof.

30. The compound of claim **17**, wherein the compound of Formula I is:



or a pharmaceutically acceptable salt thereof.

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